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The American Journal of Medicine

Vol. XVI JANUARY, 1954 No. 1

Editorial

Clinical Studies

As appropriate studies become more general, the frequency of severe hypercapnia and respiratory acidosis in patients with marked pulmonary insufficiency is becoming better appreciated and the dangers of uncontrolled oxygen therapy better recognized. Proper management of such patients requires the kind of analysis illustrated in this article. Based on their physiologic studies, the authors employed a Drinker respirator in conjunction with other measures and were able to achieve remarkable improvement in two of three desperately ill patients.

Using the cardiac catheterization technic, a study was made of the incidence of pulmonary hypertension in patients with single defects involving patencies of the atrial septum, ventricular septum or ductus arteriosus. Whereas atrial septal defect was rarely associated with significant pulmonary hypertension, this was a common accompaniment of the other two anomalies, due to increased pulmonary resistance. The significance of these associations, and of concomitant degenerative occlusive changes in the pulmonary arterioles, is discussed.

The authors contribute studies on fourteen cases of complete, anomalous pulmonary venous drainage unassociated with other cardiovascular anomalies, a unique experience. Few cases survive to adulthood. However, the findings indicate that the diagnosis can be made during life in some instances and that surgical correction may be possible. The study as a whole is of unusual interest.

Contents continued on page 5

✓	**CHECK** *pain, fever and discomfort of* COLDS, GRIPPE, FLU
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✓	*assured fluid intake*
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Review

This is a study of the complex kinetic forces involved in providing the increased pressures necessary to move air in and out of the emphysematous lung. The authors begin with an analysis of the basic mechanics of pulmonary ventilation. Pressure-flow curves obtained in normal and emphysematous subjects are then presented, the intrathoracic pressure being measured by a new type of intraesophageal pressure recording balloon. Of special interest is the authors' analysis of the limitation in maximum breathing capacity characteristic of the emphysematous patient, whose expiratory pressure-flow curve indicates a lowered maximum flow which cannot be increased by increasing pressure. This is explained by collapse of unsupported bronchioles when the pressure drop between the alveoli and the cartilage-supported end of the bronchiole exceeds the elastic pressure of the lung.

Seminars on Liver Disease

Dr. Popper introduces the seminars on liver disease with a searching analysis of the structural changes of the disordered liver and their anatomical and functional significance in liver biopsy specimens and at necropsy. After a brief consideration of the normal anatomy of this complex organ, he discusses the characteristics and meaning of liver cell degeneration, hepatocellular necrosis in its several categories, regeneration, fatty metamorphosis, cholestasis, mesenchymal (inflammatory) reaction and cirrhosis in its diverse manifestations. The concluding section dissects the aggregate abnormality of the various liver diseases into its morphologic components, with illuminating critique. This essay will be of interest to the inquiring student of liver disease.

Conference on Therapy

Conferences on Therapy (Cornell University Medical College)—This conference provides a fairly representative cross section of present thinking about current problems concerning the mechanisms

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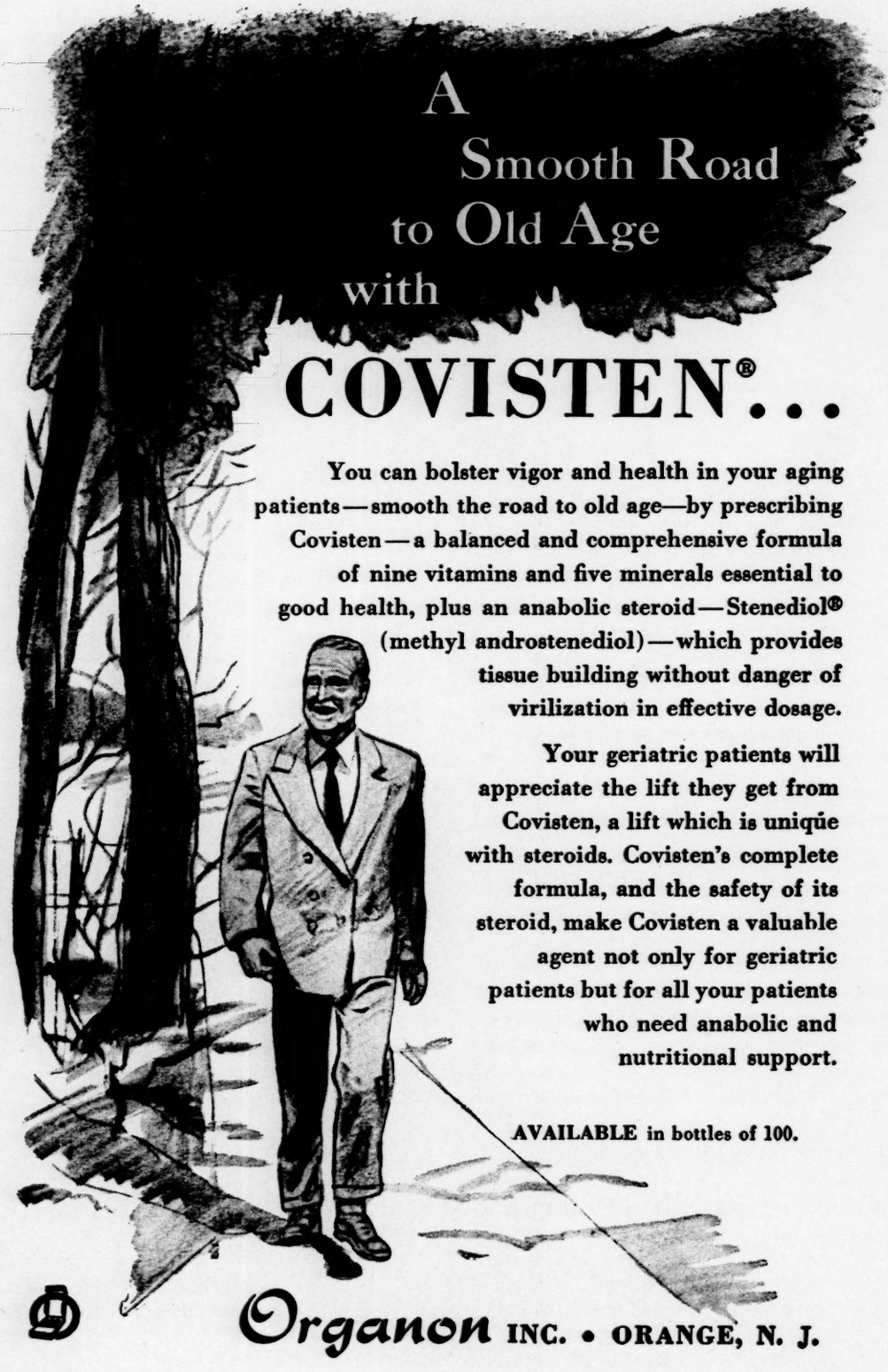

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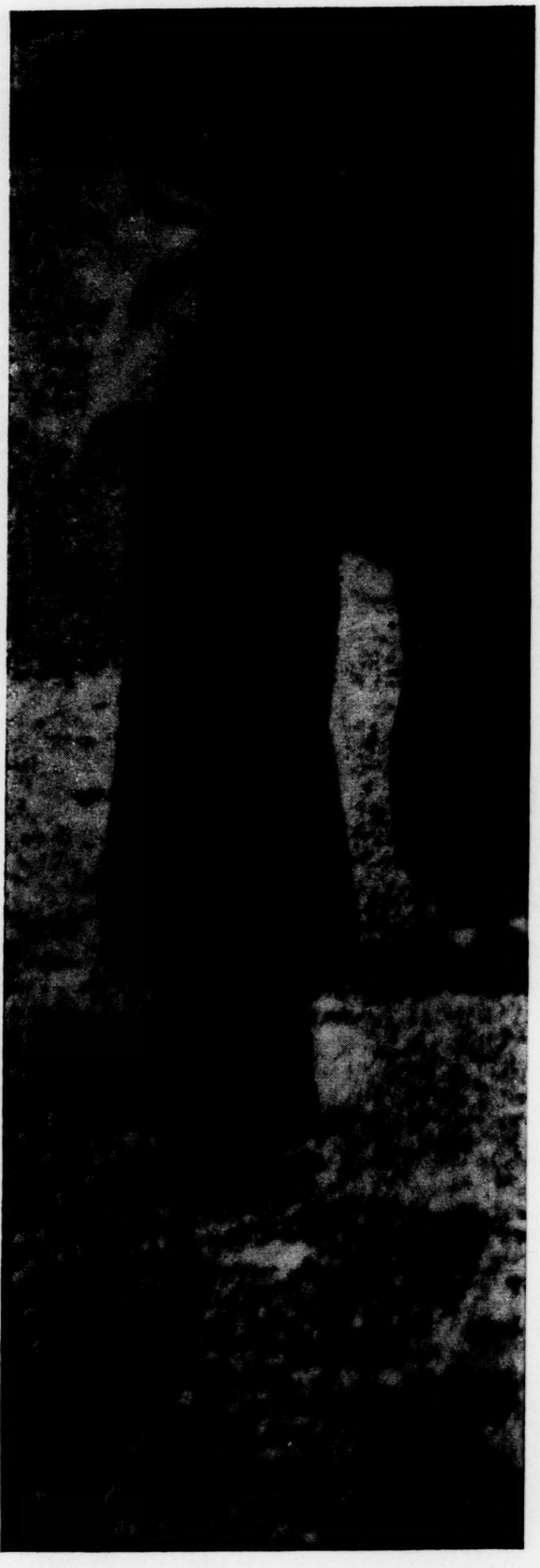
and management of congestive heart failure. Dr. Luckey opens the discussion with a balanced general presentation of the subject, which, however, reopens the schism as to the primary role of heart or kidney. A lively debate follows which does not resolve this question to the satisfaction of all but it develops that the chief points of difference are in emphasis rather than in fact, both as to mechanisms and management. Many practical problems of detailed treatment come up for informative discussion.

Clinico-pathologic Conference

Case Reports

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.



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1. Trafton, H. M., and Lind, H. E.: J. Urol. 69:315 (Feb.) 1953.
2. Blahey, P. R.: Canad. M. A. J. 66:151 (Feb.) 1952.
3. Knight, V.: New York State J. Med. 50:2173 (Sept. 15) 1950.

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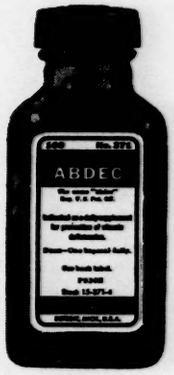

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Nitrofurantoin is useful by oral administration for the treatment of bacterial infections of the urinary tract and is indicated in pyelonephritis, pyelitis, and cystitis caused by bacteria sensitive to the drug. It is not intended to replace surgery when mechanical obstruction or stasis is present. Following oral administration, approximately 40% is excreted unchanged in the urine. The remainder is apparently catabolized by various body tissues into inactive, brownish compounds that may tint the urine. Only negligible amounts of the drug are recovered from the feces. Urinary excretion is sufficiently rapid to require administration of the drug at four to six hour intervals to maintain antibacterial concentration. The low oral dosage necessary to maintain an effective urinary concentration is not associated with detectable blood levels. The high solubility of nitrofurantoin, even in acid urine, and the low dosage required diminish the likelihood of crystalluria.

Nitrofurantoin has a low toxicity. With oral administration it occasionally produces nausea and emesis; however, these reactions may be obviated by slight reduction in dosage. An occasional case of sensitization has been noted, consisting of a diffuse erythematous maculopapular eruption of the skin. This has been readily controlled by discontinuing administration of the drug. Animal studies, using large doses administered over a prolonged period, have revealed a decrease in the maturation of spermatozoa, but this effect is reversible following discontinuance of the drug. Until more is known concerning its long-term effects, blood cell studies should be made during therapy. Frequent or prolonged treatment is not advised until the drug has received more widespread study. It is otherwise contraindicated in the presence of anuria, oliguria, or severe renal damage.

Dosage.—Nitrofurantoin is administered orally in an average total daily dosage of 5 to 8 mg. per kilogram (2.2 to 3.6 mg. per pound) of body weight. One-fourth of this amount is administered four times daily—with each meal and with food at bedtime to prevent or minimize nausea. For refractory infections such as Proteus and Pseudomonas species, total daily dosage may be increased to a maximum of 10 mg. per kilogram (4.5 mg. per pound) of body weight. If nausea is severe, the dosage may be reduced. Medication should be continued for at least three days after sterility of the urine is achieved."

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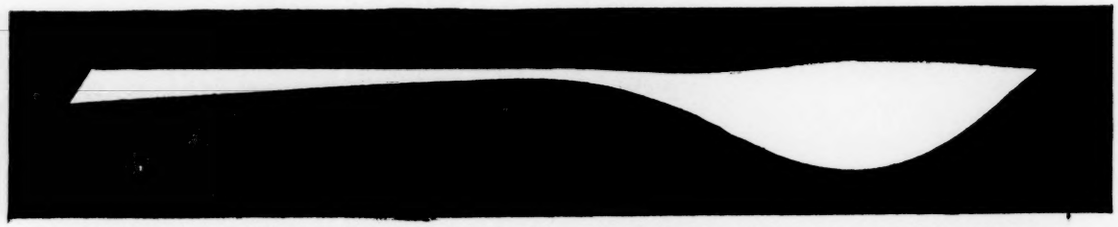

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Each teaspoonful (5 cc.) contains:

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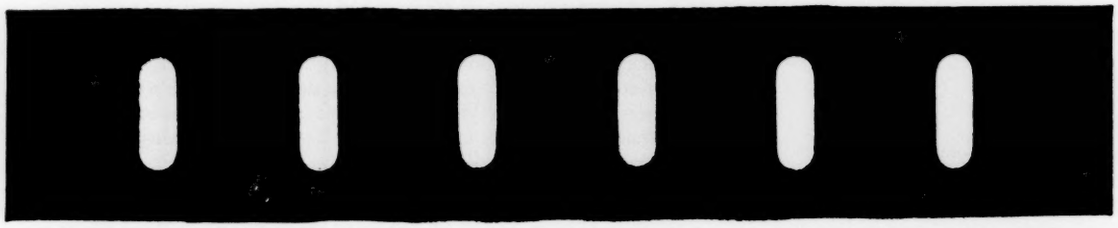
Vitamin B_{12} U.S.P. (crystalline)	4.0 mcg.	Thiamine HCl (B_1)	1.5 mg.
Extractive as obtained from of fresh gastric tissue	450.0 mg.	Riboflavin (B_2)	1.0 mg.
		Pyridoxine HCl (B_6)	0.2 mg.

Suggested Dosage: Adults: 1 to 2 teaspoonfuls. Children: ½ to 1 teaspoonful. Three times daily, or more as required. Preferably taken with food. No. 940 — Supplied in bottles of 16 fluidounces and 1 gallon.



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Gastric mucosa (dried)	100.0 mg.	Thiamine HCl (B_1)	10.0 mg.
		Vitamin C (ascorbic acid)	50.0 mg.

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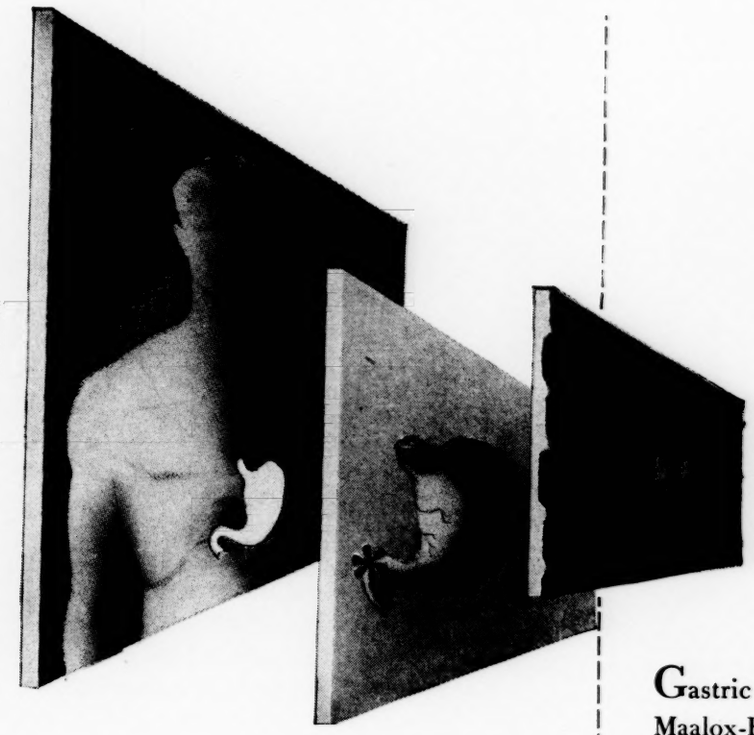

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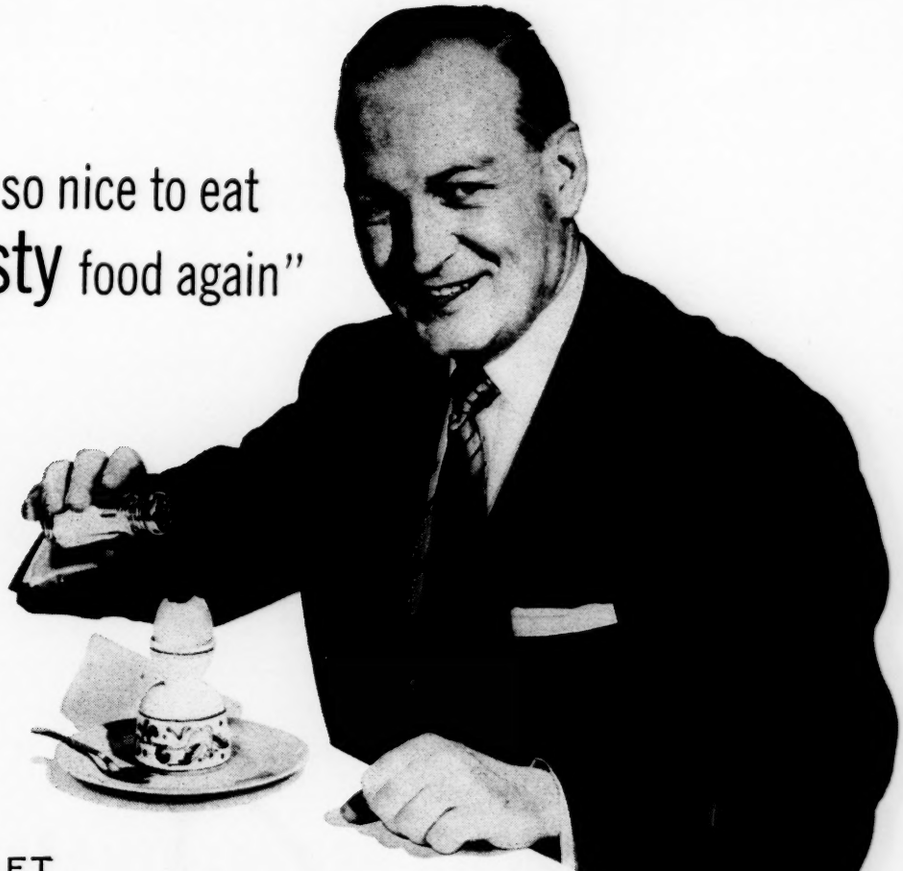
tasty food again"



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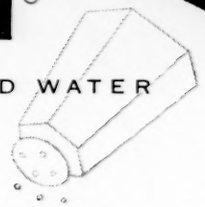

PRESCRIBE NEOHYDRIN whenever there is retention of sodium and water except in acute nephritis and in intractable oliguric states. You can balance the output of salt and water against a more physiologic intake by individualizing dosage. From one to six tablets a day, as needed.

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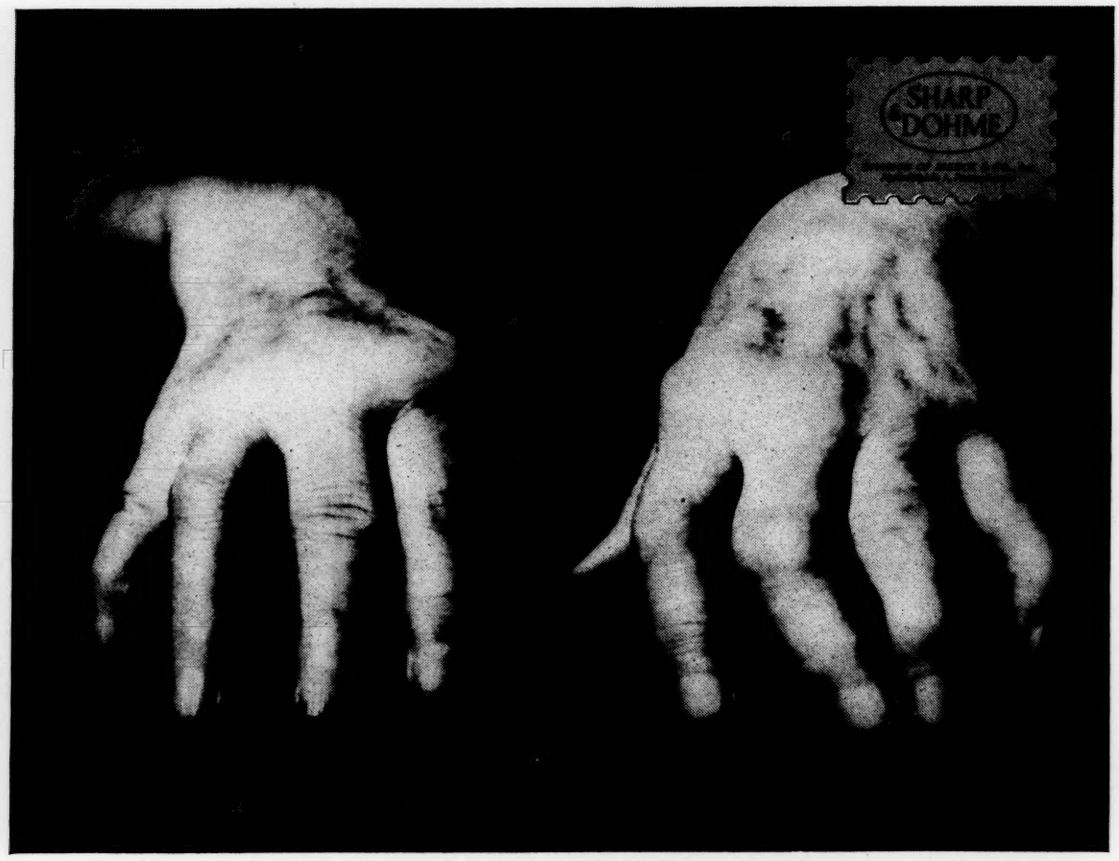

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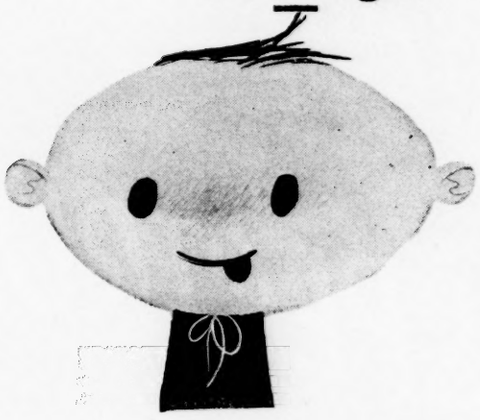

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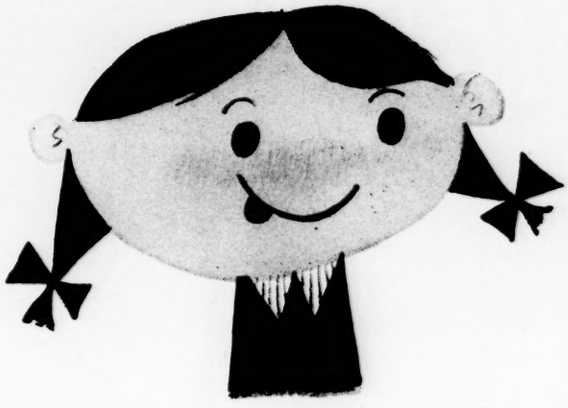

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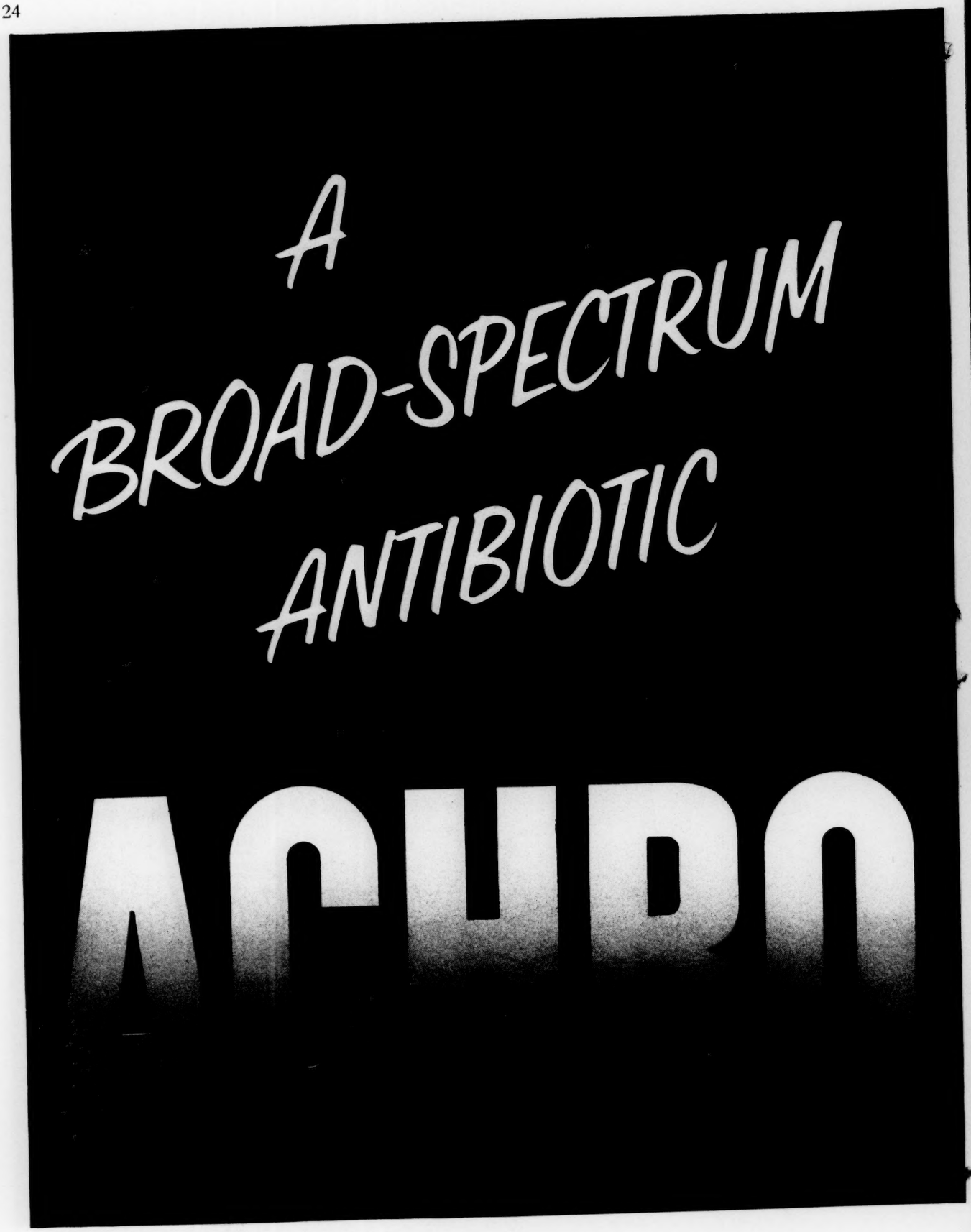
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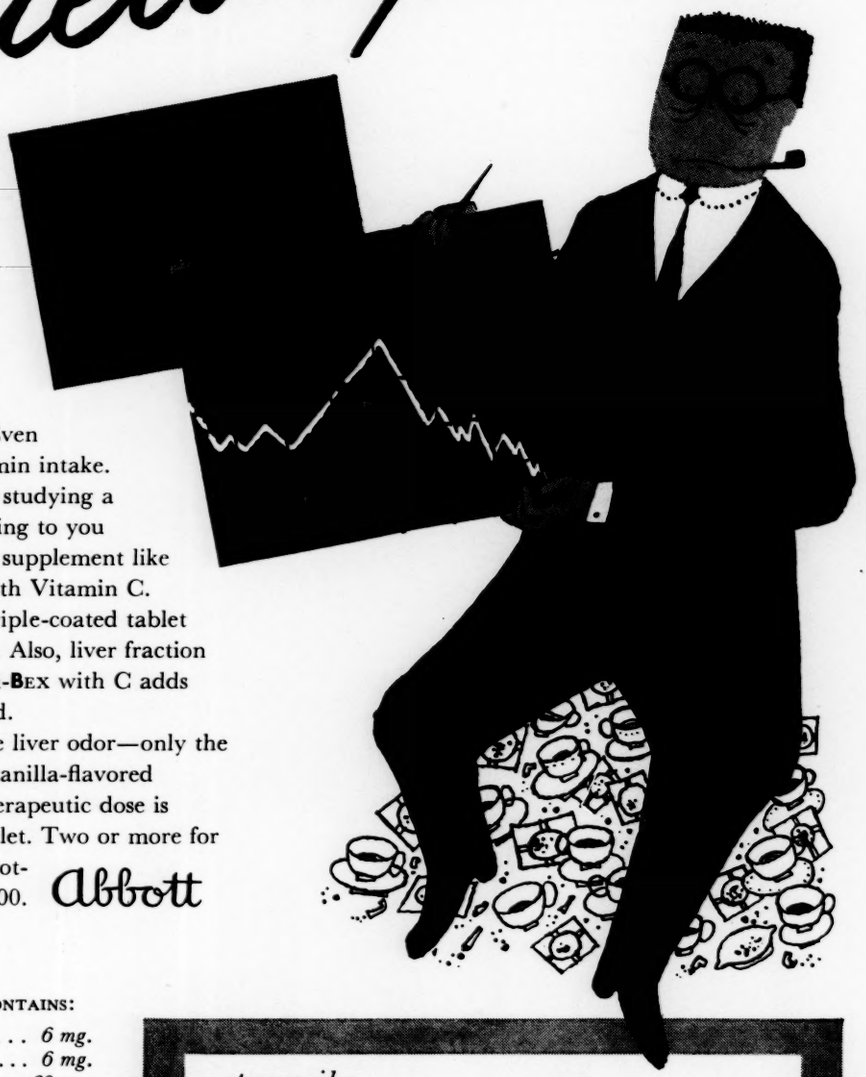

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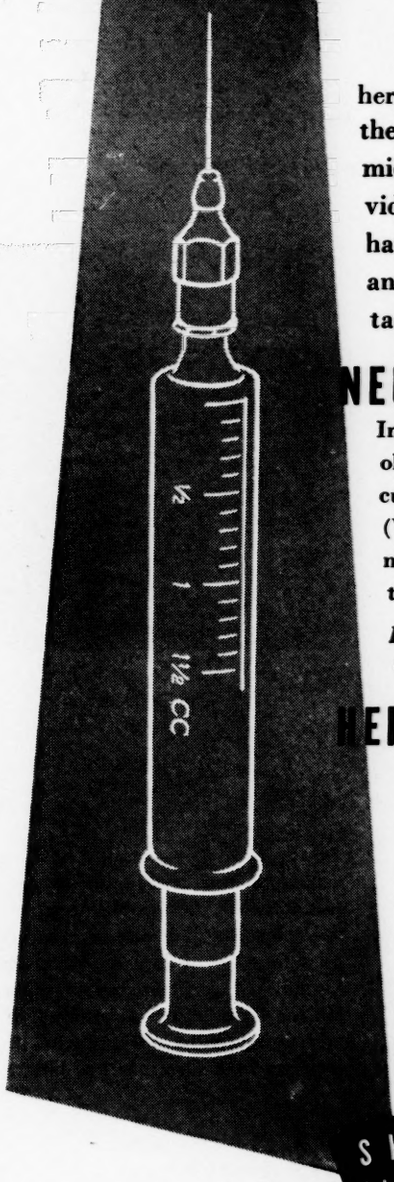
FOR THE PATIENT SEEKING RELIEF FROM NERVE ROOT PAIN



WHEN the disturbing and painful symptoms of herpes zoster, or the stinging distress of neuritis brings the patient to you, quick relief is expected. Protamide helps solve this therapeutic problem by providing prompt and lasting relief in most cases. This has been established by published clinical studies, and on the valid test of patient-response to Protamide therapy in daily practice.

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* *A folio of reprints of these studies will be sent on request.*

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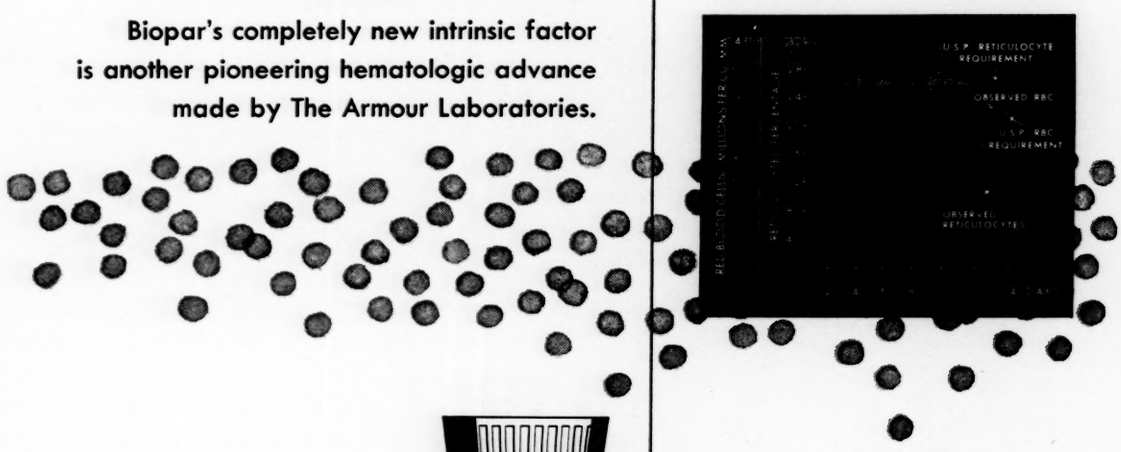

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Intrinsic Factor..... 30 mg.
Supplied: Bottles of 30 tablets.

Biopar produces prompt, positive reticulocyte and erythrocyte response in patients with pernicious anemia.

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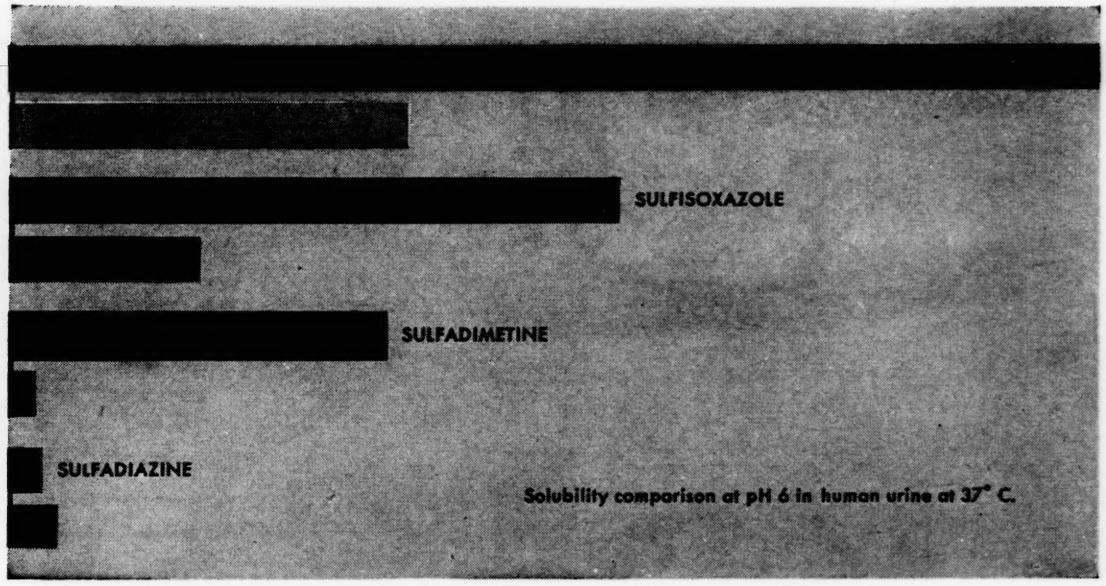

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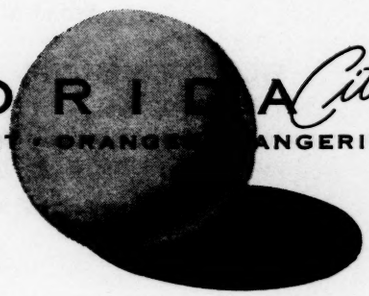

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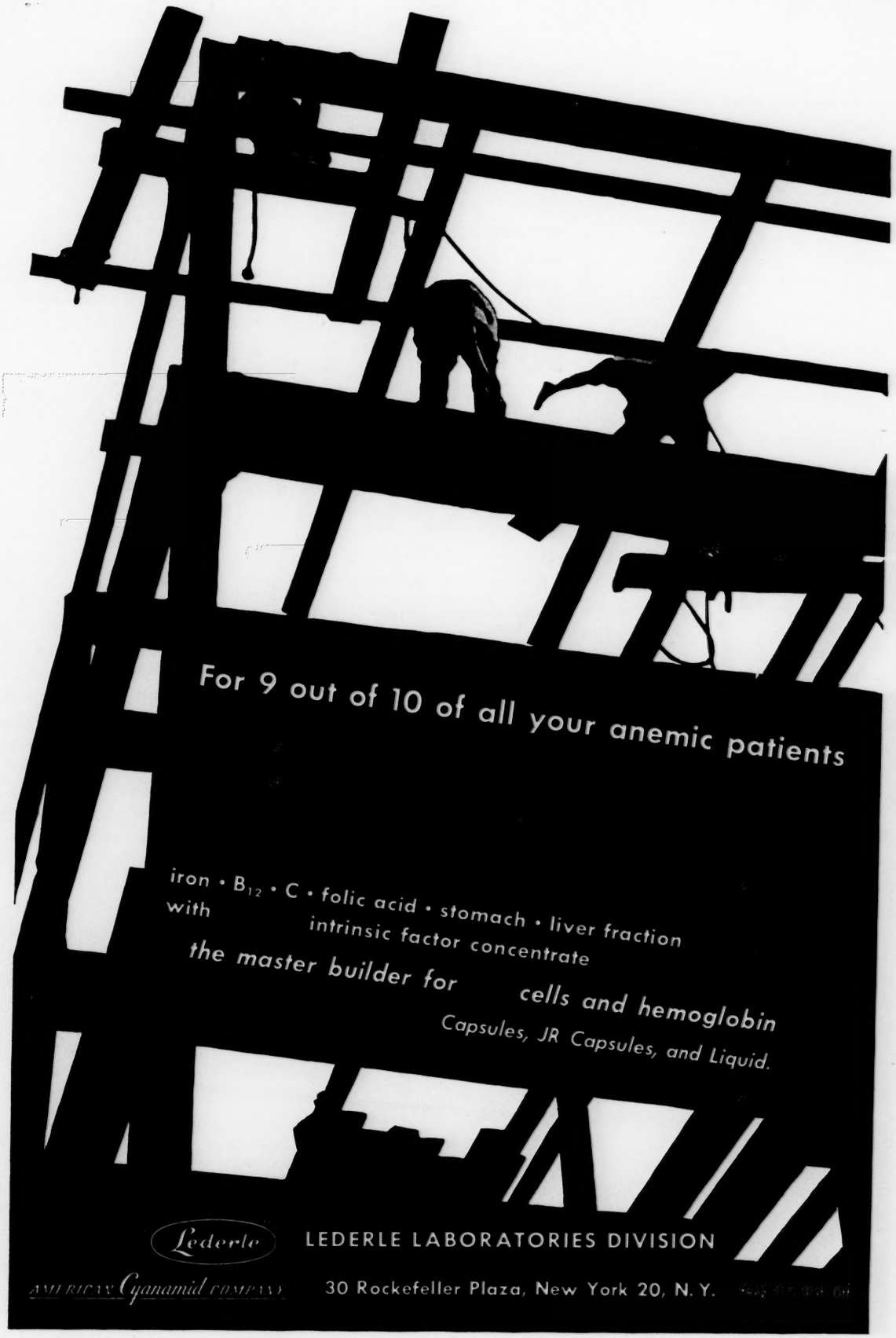
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The American Journal of Medicine

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Editorial

Salt

IN 1584 Jean de Marcounille in Paris could exclaim: "The sacredness and dignity of salt! This mineral is like unto the four elements—earth, air, fire and water, so universal, so necessary to life, it is the fifth element." De Marcounille was indisputably correct but perhaps he should have made a distinction between the salt in the diet and the salt added to the diet.

There is a growing body of evidence that salt may not be the innocuous element we suppose it to be. Selye showed that administration of large amounts of sodium chloride to chicks caused renal lesions similar to those found in human nephrosclerosis. Desoxycorticosterone causes the same type of lesions in chicks fed a "non-toxic" dose of sodium chloride. Sharp reduction of the dietary sodium prevents the production of such lesions by this steroid. Sapirstein produced renal lesions and hypertension in rats by offering only salted water for drinking. A mechanism whereby salt might cause arteriolar narrowing by causing swelling of the cells of the wall has been postulated by Eugene Stead and by Tinsley Harrison. Recent work by Tobian tends to support such a hypothesis. The Minneapolis symposium generously documents the role of salt in hypertension.

When one turns to the literature for information as to what *is* a toxic level of sodium, one finds little. There is a vast literature on this electrolyte in abnormal states and in experimental work involving sodium *and* other variables, notably the corticoids, parabiosis, etc. There is an adequate literature going at least as far back as to Pliny on the need of dietary sodium for optimal growth in farm animals. In most laboratory animals, minimal sodium requirements have been determined. There are only a few reports on the amount of salt *ingested* by humans and the data on the amount *used* take no account of the part thrown out with the cooking water. The validity of studies of "optimal" growth is uncertain, especially in farm animals, because the agriculturist is largely interested in the market weight or milk production of the young adult and little interested in pastoral geriatrics.

Experiments in which only salted water is provided represent a form of physiologic entrapment since the kidney can only rid the body of an unwanted supply by flushing it out with an excess of water. (Lord Somerville in 1817 recognized, as others had before him, that increased dietary salt requires increased water intake.) Our own work with salt in the diet and unrestricted fluid indicates that reduced fluid intake is not necessary to produce hypertension and renal and arteriolar lesions in the rat. All diets with salt substantially in excess of the Mendel, Hubbel and Wakeman recommendations induced hypertension but it required nine months to do so at the lower levels of salt feeding. Braun-Menendez summarizes " . . . all the factors which favor the retention of sodium in the organism, whether due to an increased ingestion or to a decreased excretion, facilitate the obtainment of hypertension . . . "

Since the beginning of the last century when the element sodium was discovered it has been recognized as an important constituent of the body and an essential element in the diet. Redtenbacher and Carl Schmidt first paid scientific attention to salt in disease states about 1850 and during the ensuing hundred years we have discovered and rediscovered the merit of salt withdrawal in edema, heart failure and hypertension.

Over recent years we have learned to handle some difficulties encountered during salt restriction and have developed an awareness of its hazard when the kidney is incompetent. Despite this, we have paid amazingly little attention to dietary salt in the apparently normal and especially the young, for the evidence indicates a greater sensitivity to sodium in youth. The human appetite for salt has become

disengaged from the need for it and the amount employed by a given individual is almost wholly governed by culture, custom and the food habits ingrained through early life. It is appropriate to look back to the origins of the human use of added salt and reappraise our taste for this material which Hakluyt reports the Icelanders of the 16th century called "the provocation of gluttony."

Recorded history of the human use of salt goes back through the shades of time at least to the Phoenicians, who engaged in a lively trade in it. The Trojans freely used it 3,000 years ago. The ready supply of salt in the hot Mediterranean countries was widely utilized in biblical times. As far back as our records go, we find salt in use. Despite this, from earliest times to the present it was also known that there were areas where salt was not used. The Odyssey speaks of the inlanders of Epirus who do not know the sea and use no salt. As recently as forty years ago the Bedouins of Hadramut were reported as unaccustomed to salt. Among American Indians Kroeber finds ". . . the outstanding fact regarding salt in native western North America is that it was used in half that area (the southern part) and not used in the other half (the northern part). The line of demarkation is sinuous but there were virtually no exceptions to the rule that salt was eaten everywhere to the south and not eaten everywhere to the north of this line."

Despite the widespread use of salt, there have been a number who doubted the need for it in the quantities that custom dictated. Swift wrote "I am confident that the frequent use of salt among us is an effect of luxury" and at one point made his imaginary traveler Gulliver a convert to doing without it. The explorer Stefansson reported "It was here (among the Eskimoes) that I learned from experience what I already knew theoretically, that [added] salt is not necessary for health and that the desire for it disappears in about three months when one is without it."

It is evident that appetite for salt as such exists, for rats on a salt deficient diet will avidly lick at every finger print on their cages and pans. Above this it appears that, once accustomed to its use, the human craving for it is intense and we do not lack evidence that men took strong views about it. The Teutons waged wars for saline streams. Wives and children were sold into slavery to obtain it. Decapitation or dismemberment was sometimes the penalty for carrying salt out of ancient cities. Governors early employed taxation of salt to raise money and some of the bitterest passages of English history from the sixteenth to the nineteenth century trace the taxation of salt and the misery and misgovernment attending it. In 1785 the Earl of Dundonald wrote "Every year in England, ten thousand people are seized for salt smuggling and three hundred men are sent to the gallows for contraband trade in salt and tobacco."

Salt was in wide use by the beginning of recorded history. We must therefore look farther back in time for clues to its introduction. As everyone knows, the herbivores will travel long distances to reach salt licks but, what is less well known, the carnivores do not. The evidence indicates that humans in their first, cave dwelling era were carnivorous, probably small mobile bands of hunters and fishermen. One of the oldest centers of human habitation was in what is now northern Iraq where recent investigations of Barda Balka, Zarzi, Palegawra, Karim Shahir and Jarmo give revealing evidence by residual artifacts and the radioactive carbon-dating method that the transition from the earliest tool-using and food-gathering stage, which began at least 500,000 B.C., to the animal domestication and incipient agriculture stage, i.e., the "food producing revolution" began about 6,000 B.C. and that by 4,600 B.C. the era of primary peasant efficiency with permanent villages, pottery, metal and weaving was established. This change from a hunting and nomadic existence to an organized peasant life was marked by a sharp change from a roasted meat and milk product diet to one in which vegetables and cereal grains predominated. A nomadic diet of flesh and milk did not require any added salt but as cereal grains and vegetables took their place in the diet, added salt became a necessity. Curiously this does not seem to be due to a lesser amount of sodium in this diet but to a vastly larger amount of potassium. While a nomadic diet of meat and milk contains four or five times as much potassium as sodium, a cereal and vegetable diet contains twelve to twenty times as much potassium as sodium. The physiologic reason for the added salt requirement on a cereal-vegetable diet remains obscure although this observation was made over a century ago.

Oblique evidence that the origin of the human

use of added salt began concurrently with the change from nomadic to agricultural existence may be derived from linguistics. It is not possible to trace a common word for salt farther back than primitive Greek. There is no word for salt in ancient Sanskrit, the oldest of the Indo-European languages. The same is true of terms for farming. While common roots from nomadic life for the herd, the cattlefold, the herdsman and the milking time occur in rich profusion, terms such as for the plow, tilling and other more advanced agricultural activities do not share common roots, suggesting strongly that these, too, were of much later introduction.

It would seem that primitive man developed his craving for salt concurrently with his progress from a nomadic to an agricultural existence, that soon thereafter the preservative properties of salt were observed and exploited. Widespread use of salted foods may well have played an important role in dissociating the human taste for salt from the need for it. Life expectancy was short in those days and man was grateful to survive from season to season. The fact that the preservative value of salt depends upon its relatively higher toxicity for lower forms of life troubled him little and he was more concerned with keeping his blood inside him than with the pressure it might attain in his middle age. Over the tens of centuries that have since elapsed the taste for salt and the need for it underwent a progressive dissociation to the present time when every cafeteria table supports what once was a prince's ransom of snowy white salt.

Certain it is that salt is a dietary essential but there is an urgent need to re-examine the human requirement for it, its evident relation with potassium intake, its native toxicity and to try to unravel the dissociation between taste and need.

There is an entertaining passage in Robinson Crusoe where Daniel Defoe describes the stranded man's effort to induce Friday to eat salt. This stalwart "spat and sputtered at it, washing his mouth with fresh water after it." Had Friday had access to the current medical literature, he would perhaps even more steadfastly have withstood Crusoe's blandishments, grimaces and sign language.

GEORGE R. MENEELY, M.D.

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Clinical Studies

Pulmonary Hypertension*

III. Physiologic Studies in Three Cases of Carbon Dioxide Narcosis Treated by Artificial Respiration

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THE syndrome of coma in chronically anoxic patients with pulmonary emphysema receiving oxygen therapy has recently been described.[1–5] These patients have severe hypercapnia associated with hypoventilation. As a result of advanced pulmonary emphysema and fibrosis, the ventilatory function of the lungs is impaired and the carbon dioxide tension of arterial blood rises. The respiratory center, which is normally exquisitely sensitive to small changes in the partial pressure of CO_2 ($P_{a_{CO_2}}$), becomes adjusted to high tensions of CO_2. In these patients the stimulus to breathing results, in part, from the effects of anoxia on the chemoreceptors in the aortic and carotid bodies. When oxygen therapy is given to these patients, the hypoxic stimulus is removed resulting in further hypoventilation and more CO_2 retention. Thus a vicious cycle is initiated which results in a difficult therapeutic problem.

Carbon dioxide retention is the primary problem in this syndrome and ventilation has to be increased to restore homeostasis. Since these patients have lost the normal "centrogenic" and "chemoreflexic" drives for breathing,[6] some mechanical aid to ventilation must be employed. Motley advocated the use of an intermittent positive pressure respirator to increase the minute ventilation and to remove the excess carbon dioxide.[7] Our experience with the "pneophore" apparatus in severely dyspneic patients has been discouraging. Recently, Boutourline-Young and Whittenberger reported two cases of pulmonary emphysema with hypercapnia and anoxia whom they treated in the body respirator.[8] One of these patients died but the other recovered completely and returned to his former occupation. More recently, Stone et al. have reported the results of artificial respiration in the successful treatment of CO_2 retention in three cases of chronic pulmonary disease.[9]

This report concerns the treatment of three patients with marked pulmonary insufficiency by means of the body respirator. One of these patients subsequently died, but it is believed that without this therapy the other two would certainly not have survived.

METHODS

Cardiac catheterization was carried out by a modification of the method of Cournand and Ranges.[10] Oxygen consumption was measured using a continuous gas analyzer previously described.[11] Arterial blood samples were collected in heparinized syringes, cooled and analyzed for respiratory gas content according to the method of Van Slyke and Neil.[12] Arterial blood gas tensions were determined in duplicate according to the method of Riley.[13] Arterial blood pH was calculated from Singer and Hasting's nomogram[14] and determined directly in Case III and in two instances in Case I when the $P_{a_{CO_2}}$ was extremely high. Arterial blood samples for

* From the Chest Laboratory of the Department of Medicine of the University of Rochester School of Medicine and Dentistry, and the Medical Clinics of Strong Memorial Hospital and Rochester Municipal Hospital, Rochester, N. Y. This study was supported in part by a grant-in-aid from the National Heart Institute of the National Institutes of Health, Public Health Service, and by the Hochstetter Fund and Ernest L. Woodward Fund.

direct pH determination were drawn in separate heparinized syringes and analyzed immediately in a Cambridge pH meter according to the method of Wilson.[15] Mean pressures were determined by planimetric integration of pressure tracings from direct writing oscillograph records of the output from strain gauge manometers.* Partition of the lung volume was performed by a helium dilution method.[16]

CASE REPORTS

CASE I. M. H. (No. 136356) was a seventy-one year old widow admitted to the Strong Memorial Hospital on September 11, 1951, with a history of chronic cough, dyspnea, orthopnea and ankle edema for several years. Her admission was prompted by weakness and mental confusion of several days' duration. Her first visit to this clinic was thirteen years previously for acute and chronic bronchitis and intrinsic asthma. At that time the vital capacity was reduced to 1.1 L. During the past several years she had had several admissions for either acute bronchitis or bronchopneumonia and cardiac failure for which she had been treated with digitalis and mercurial diuretics. In 1947 the vital capacity was further reduced to 0.8 L. and the CO_2 combining power was elevated to 35 mM./L.

Significant findings on admission were a fever of 38.3°C., rapid and shallow respirations, weakness, mental confusion, cyanosis and orthopnea. The chest showed a marked increase in the anteroposterior diameter with coarse rhonchi throughout both lung fields and a few fine inspiratory rales at the left base posteriorly. The heart was enlarged to the left with a normal rate and rhythm. There was a grade 3 apical systolic murmur as well as accentuation of the second pulmonic sound. The liver was palpable 3 cm. below the costal margin and there was 2+ pitting edema of the lower extremities. The initial laboratory study showed a white blood count of 15,900 with a normal differential count, hematocrit 54 per cent and hemoglobin 16.7 gm. per cent. Blood chemistries showed a CO_2 combining power of 40 mM./L., chlorides 93 mEq./L., normal serum sodium and normal blood urea nitrogen.

Because of cyanosis and respiratory distress, oxygen therapy by nasal catheter was instituted. On the following day arterial blood gas analysis revealed an oxygen saturation of 91 per cent and a CO_2 content of 32.9 mM./L. Oxygen was discontinued for twenty minutes and another arterial blood-gas analysis revealed oxygen saturation of 55 per cent and a $P_{a_{CO_2}}$ of 91 mm. Hg. The CO_2 content did not change materially. After two days of continuous nasal oxygen administration the patient had become semi-

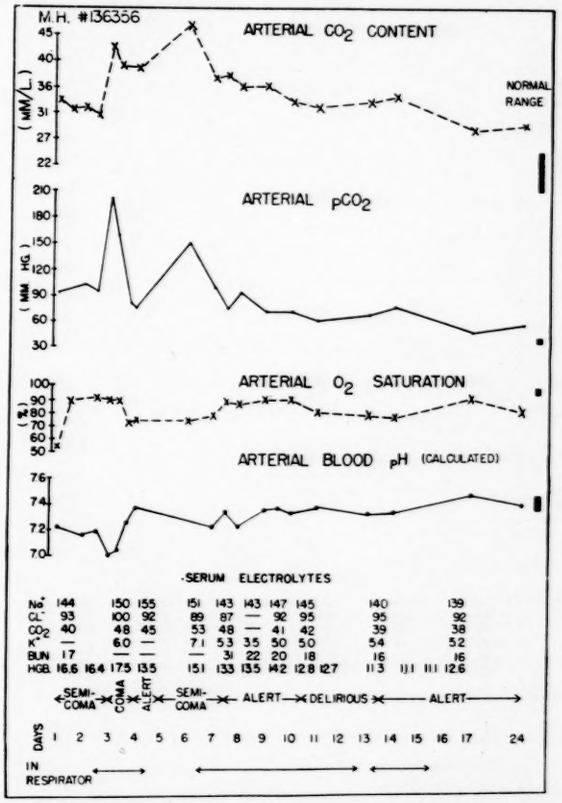

FIG. 1. Case I. Serial blood studies during patient's hospital course. Oxygen therapy was administered continuously except on the first and last days. The pH values on the third hospital day were determined directly.

stuporous and her condition appeared precarious. Because of the pronounced hypercapnia associated with a semicomatose state it was decided that mechanical ventilation should be attempted in order to blow off carbon dioxide. This decision was hastened by the finding of a $P_{a_{CO_2}}$ of 103 mm. Hg and an arterial blood pH of 7.16 indicating marked uncompensated respiratory acidosis. The patient was placed in the Drinker respirator.

Figure 1 graphically shows the results of serial studies of arterial blood gases and pH. At first, both clinically and chemically the patient's condition deteriorated. She became unresponsive as the CO_2 retention advanced. Despite the use

* Statham Laboratories, Inc.

of the body respirator, respiratory excursions were not improved. On the following day a pharyngeal airway was introduced. Within an hour there was dramatic improvement and the patient became alert and oriented. Coincident with clinical improvement the pH rose from 7.04 to 7.37 and the $P_{a_{CO_2}}$ dropped from 159 to 82 mm. Hg. At the same time the arterial oxygen saturation which had been around 90 per cent suddenly dropped to 74 per cent where it remained for the following five days. In retrospect, the patient had probably developed some degree of atelectasis as a result of bronchial aspiration. Figure 1 demonstrates the patient's deterioration when she was removed from the respirator for several days. However, after being returned to the respirator improvement again resulted and was maintained. A further complication occurred on the tenth hospital day when she became delirious and remained disoriented for three days. During this period there was no material change in the blood chemistry and no obvious reason for the change in her mental status. However, she had been given 32 mg. phenobarbital on the night prior to the onset of delirium. On the fifteenth hospital day she was removed from the respirator and has since received no therapy other than digitalis and a low-salt diet. She is able to do light housework and her own cooking, but her exercise tolerance is considerably limited because of exertional dyspnea.

TABLE I
CARDIAC CATHETERIZATION STUDIES

	Case I		Case II		Case III			
	(Breathing Air) Post-treatment		(Breathing Air) Post-treatment		(Breathing O_2) Pre-treatment		(Breathing Air) Post-treatment	
	Brachial Artery	Pulmonary Artery	Brachial Artery	Pulmonary Artery	Brachial Artery	Pulmonary Artery	Brachial Artery	Pulmonary Artery
Blood Gas Analysis:								
CO_2 content (vol. %)	77.2	80.4	64.4	66.1	85.1	87.9	51.4	53.8
O_2 content (vol. %)	8.6	5.2	14.6	10.3	12.8	8.7	15.6	11.9
O_2 capacity (vol. %)	15.1	.....	15.7	.....	25.31	.....	18.0	.....
O_2 saturation (%)	57.2	38.4	92.8	65.4	50.5	34.5	86.7	66.2
pH	7.51	.....	.....	.....	7.25	7.19	7.42	7.37
$P_{a_{CO_2}}$ (mm. Hg)	79	.....	45	.....	77	.....	48	.....
$P_{a_{O_2}}$ (mm. Hg)	37	35	60	41	39	21	59	41
Pressures (mm. Hg):								
Systolic/Diastolic	.....	42/22	114/73	22/17–46/20	.....	67/26–91/50	132/80–147/88	38/10–51/20
Mean	.....	25.9	92.9	26.9	.....	60.0	100	28.9
Cardiac Output:								
O_2 consumption (cc./M^2/min.)	114		164		....		136	
A–V O_2 difference (vol. %)	3.43		4.30		4.05		3.65	
Cardiac index (L./M^2/min.)	3.32		3.81		....		3.72	
Resistance (dynes-sec.-cm.$^{-5}$):								
Total pulmonary	451		410		....		394	
Pulmonary arteriolar	....		348		....		227	

The results of cardiac catheterization on the fifteenth hospital day are summarized in Table I. There was moderate pulmonary hypertension, the arterial oxygen saturation was materially reduced and the carbon dioxide content and $P_{a_{CO_2}}$ were significantly elevated over the values obtained during the previous few days. This was undoubtedly due to hypoventilation associated with the discomfort of the face mask. It is possible that the mean pulmonary artery pres-

sure was elevated partly as a result of the anoxia and hypercapnia produced in this way.[17]

Case II. J. M. (No. 336249) was a fifty-two year old white unemployed painter whose admission on November 8, 1951, was prompted by severe, progressive dyspnea and weakness. He had a history of increasing shortness of breath over the past eight years and had not worked for two years. He had been bedridden during the previous month because of severe dyspnea and fatigue. During the past year he had been using several aminophyllin suppositories daily and had employed an adrenalin nebulizer with increasing frequency. There was no history of orthopnea or hemoptysis, and except for slight ankle edema which had disappeared when he was confined to bed, there were no other cardiorespiratory symptoms.

Physical examination revealed normal temperature and blood pressure, with a pulse of 120/minute and a respiratory rate of 40. The patient appeared cachectic and chronically ill with obvious dyspnea but no orthopnea. Respirations were rapid and shallow, and there was marked cyanosis of the mucous membranes, skin and nails. The antero-posterior diameter of the thorax was increased and during inspiration there was marked retraction of the supraclavicular and suprasternal fossae as well as the lower rib interspaces. The lungs were hyperresonant to percussion with distant breath sounds and a few rales at the right base. Examination of the heart was not remarkable except for difficulty in defining the left border. The sounds were distant. The liver edge was 2 cm. below the costal margin by percussion. Pertinent laboratory studies showed red blood count, hemoglobin and hematocrit of 6.4 million, 19 gm. per cent and 58 per cent, respectively. The CO_2 combining power was 37 mM./L. and blood chloride 88 mEq./L. The electrocardiogram showed right axis deviation, sinus tachycardia with a rate of 110 and low T waves throughout the limb and chest leads.

For the first three days in the hospital no specific therapy was instituted other than supportive treatment. Oxygen was purposely withheld until the fourth day when it was started by nasal catheter at the rate of 1 L./minute. Despite the slow rate of administration the patient was found in coma on the following morning. Within half an hour after oxygen was discontinued the patient was able to respond to simple questions. Following this his mental condition gradually cleared although arterial blood gas studies showed severe hypercapnia and hypoxemia. Consequently, it was decided to ventilate the patient artificially in the Drinker respirator.

Figure 2 shows the results of serial arterial blood gas analyses. There was no immediate benefit from this therapy. Because of tenacious tracheal secretions beyond the reach of a suction catheter the patient was removed from the respirator for three days. On the eleventh hospital day he was placed back in the respirator because of increasing respiratory distress, cyanosis and apprehension. Positive and negative intratank pressures and the rate of respiration were increased on the thirteenth hospital day because of failure to improve. In addition, oxygen therapy was discontinued. Following this $P_{a_{CO_2}}$ soon fell to a slightly elevated level. The patient's condition seemed static and he was removed from the respirator on the twenty-first hospital day. Clinically, he had improved since admission but continued to be quite dyspneic at rest and was necessarily confined to bed.

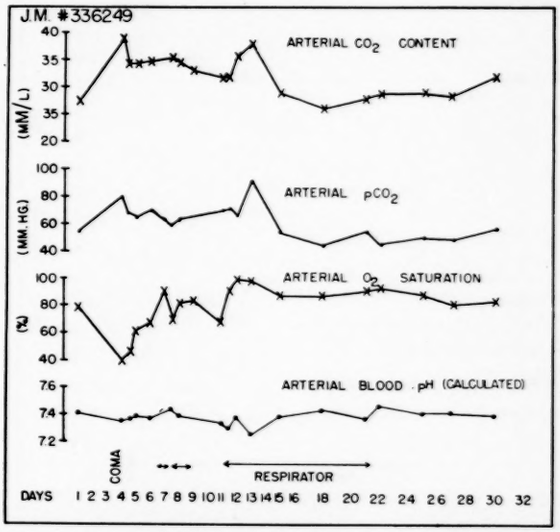

Fig. 2. Case II. Serial arterial blood studies throughout patient's hospital stay. Coma on the third hospital day resulted from several hours of oxygen administration at the rate of 1.0 L. per minute. The second arterial blood was drawn thirty minutes after oxygen had been withdrawn.

On the twenty-second hospital day a cardiac catheterization was undertaken. The results of this procedure are shown in Table I.

Lung volume determinations are shown in Table II. There is a marked increase in the

residual volume indicating emphysema. The vital capacity was considerably reduced and because of the marked increase in the absolute residual volume the ratio of residual volume to total capacity was greatly increased.

Because the patient continued to be extremely dyspneic at rest, and because favorable results had been obtained in similar but less severely disabled patients it was decided to institute pneumoperitoneum. The initial injection of 100 cc. of air into the peritoneal cavity was well tolerated. Two days later another 200 cc. of air were injected slowly into the peritoneal cavity. At the end of this injection the patient complained of upper abdominal pain and rapidly became dyspneic and cyanotic. He expired shortly because of respiratory failure.

A postmortem chest x-ray failed to show pneumothorax. Postmortem examination showed no cause for his sudden death. In particular no evidence of air embolism could be demonstrated. There was marked emphysema of the lungs with massive pleural adhesions of the left lung. The heart was small but there was definite right ventricular hypertrophy.

TABLE II
PARTITION OF LUNG VOLUME (L.)

	Case I		Case II		Case III	
	Observed	Predicted (%)	Observed	Predicted (%)	Observed	Predicted (%)
Vital capacity	0.74	35	1.37	38	1.25	46
Expiratory reserve volume	0.19	...	0.43	...	0.41	...
Residual volume	1.18	124	5.68	353	1.36	168
Total capacity	1.92	63	7.05	136	2.61	74
$\frac{\text{R. V.} \times 100}{\text{T. C.}}$	62%	...	81%	...	50%	...

CASE III. E. T. (No. 350528) was a forty-two year old housewife admitted to the hospital on September 13, 1952, for the first time with complaints of shortness of breath and ankle swelling. She had a history of year-round bronchial asthma with frequent acute exacerbations associated with upper respiratory infections. For the past four years she had noted progressive dyspnea on exertion. Five months prior to admission she developed ankle edema which did not respond to digitalis and salt restriction. Shortly before admission she was treated for these symptoms in another hospital with oxygen, mercurial diuretics and low-salt diet with only temporary improvement. A chronic cough productive of a small amount of greenish sputum had been present for years.

Physical examination revealed a well developed, alert, obese woman who was moderately dyspneic and cyanotic at rest. There was no orthopnea, but pitting edema (3+) was present over both shins. The temperature was 37.8°C. rectally. The neck veins were moderately distended. There was some dullness to percussion at both lung bases where rales were present. Numerous wheezes and rhonchi were heard throughout both lungs. The heart was slightly enlarged to the left by percussion, but was otherwise normal except for a tachycardia of 138/minute. The liver edge was not palpable.

Laboratory tests showed 1+ albuminuria, blood chloride and CO_2 combining power of 90 mEq./L. and 42 mM./L., respectively. Venous pressure was 270 mm. of water and arm to tongue and arm to lung circulation times were 20 and 14 seconds, respectively. The hemoglobin was 19.0 gm. per cent.

She was given a low-salt diet, expectorants, aminophyllin by vein, demerol for apprehension, and oxygen at a slow rate by mask. Digitalis was continued. Early in the morning after admission oxygen flow was increased to 7 L./minute because of increased respiratory distress and cyanosis. Several hours later she became comatose. Later that day arterial blood samples were drawn while the patient was breathing room air and again after about thirty minutes of breathing CO_2 by mask at 2 L./minute. The results are shown in Table III. The oxygen saturation

of her arterial blood rose appreciably on O_2 therapy, but the $P_{a_{CO_2}}$ increased further and respiratory acidosis ensued.

On the following day cardiac catheterization was performed, the results of which are presented in Table I. Pulmonary hypertension was severe, the mean pulmonary artery pressure measuring 60 mm. Hg. The mean "pulmonary capillary" pressure was normal (7 mm. Hg). Therefore, the pulmonary hypertension can be classified as precapillary.[14] The right ventricular end-diastolic pressure (8 mm. Hg), and the mean right auricular pressure (10 mm. Hg) were elevated, indicating right ventricular failure. These measurements were obtained while the patient was breathing O_2 through a face mask at the rate of 2 L./minute. Oxygen was withdrawn for fifteen minutes and serial pulmonary artery pressures were recorded. There was an insignificant fall in the mean pulmonary artery pressure. The arterial blood oxygen saturation fell at the end of this period to 38.3 per cent but hypercapnia did not increase. Unfortunately, it was not possible to estimate the cardiac output.

Because the patient had not improved she was placed in a body respirator on the fourth hospital day. Her subsequent course, followed by arterial blood gas studies, is shown in Figure 3. At first the patient had difficulty synchronizing with the respirator. She attempted to maintain a respiratory rate of about 30/minute. As a consequence her condition deteriorated chemically. However, with training and by increasing the rate and inspiratory and expiratory pressures of the respirator the CO_2 retention and respiratory acidosis gradually improved. One week after being in the respirator O_2 therapy and mechanical respiration were discontinued intermittently. By the eighteenth hospital day the patient was markedly improved and all treatment other than digitalis was stopped. She was discharged to her home four days later after the lung volume had been partitioned. These studies (Table II) indicated the presence of predominant pulmonary fibrosis.

TABLE III

ARTERIAL BLOOD GAS STUDIES IN CASE III BEFORE AND DURING OXYGEN THERAPY

Breathing	$P_{a_{CO_2}}$ (mm. Hg)	$P_{a_{O_2}}$ (mm. Hg)	CO_2 Content (vol. %)	O_2 Content (vol. %)	O_2 Sat. (%)	pH	
						Calculated	Observed
Room air	79	24	36.9	8.55	33.7	7.36	....
Oxygen by mask 2 L./minute for 30 minutes	97	54	36.7	18.66	73.5	7.25	7.26

Another cardiac catheterization was carried out two and one-half months later. The results are summarized in Table I. In comparison with the pretreatment values there was striking improvement in almost every respect. The mean pulmonary artery pressure had fallen from 60 to 29 mm. Hg and there was an associated rise in the oxygen saturation of the arterial blood. The $P_{a_{CO_2}}$ and oxygen capacity of the blood (Hgb.) had declined to normal. Respiratory acidosis had been corrected. As in the two earlier cases the cardiac index was normal, but the total pulmonary resistance was elevated. The pulmonary arteriolar resistance was also somewhat above normal.

Comment. Two of the three patients recovered and have less respiratory distress than in the past several years. The death of the patient in Case II was unfortunate but he failed to respond as favorably as the other patients and it was apparent that he would remain a respiratory cripple.

The clinical and laboratory findings of all three cases were similar in the following respects: (1) Clinically each patient had severe dyspnea, cyanosis and tachypnea at rest. All had a history of chronic respiratory difficulty which had recently been accentuated. Shortly after admission, oxygen given because of severe respiratory distress resulted in loss of consciousness. (2) Laboratory studies revealed severe hypercapnia, hypoxemia and respiratory acidosis. In addition, polycythemia (hemoglobin 16.6–18.9 gm. per cent) was present. Lung volume studies (after treatment) demonstrated that the pulmonary

insufficiency was mainly due to pulmonary fibrosis in Cases I and III and to severe emphysema in Case II. Case II did not do well. Both cases of Boutourline-Young and Whittenberger had severe emphysema and one of these improved strikingly following mechanical ventila-

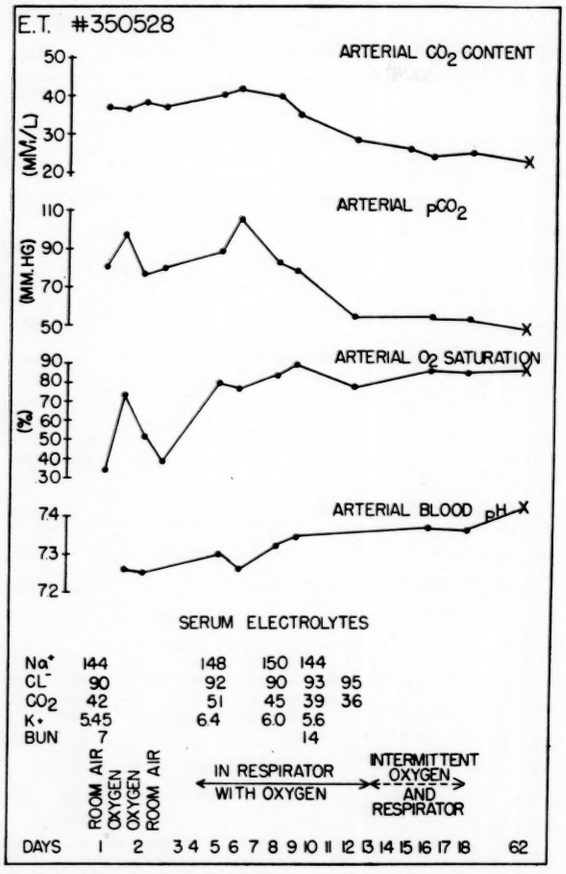

FIG. 3. Case III. Serial blood studies during and two months following hospitalization. The pH values were all determined directly.

tion therapy.[8] (3) Cardiac catheterization after therapy revealed moderate pulmonary hypertension in each case associated with normal cardiac output and a moderate increase in total pulmonary resistance. The most striking finding related to cardiac catheterization was the markedly elevated pulmonary artery pressure in Case III prior to therapy. (4) The clinical response to mechanical ventilation was slow in every instance. An average of nine to ten days in the respirator was required before chemical improvement stabilized. All patients fought the respirator for several days. Case I was in the respirator for more than a day before it was realized that she needed a pharyngeal airway. Even after respiratory acidosis had compensated, several days were required for the respiratory center to become adjusted to the relatively normal CO_2 tension. This may reflect the severity of hypercapnia in two of our cases.

OBSERVATIONS

The pathologic physiology and physiologic basis for therapy have been adequately discussed elsewhere.[8] A small number of severely emphysematous patients may develop marked hypercapnia. Continuous O_2 therapy is dangerous in these patients and is associated with increased cerebrospinal fluid pressure and further increment in the arterial CO_2 tension.[18] It is not clear why this syndrome does not occur in all patients with severe emphysema. Boutourline-Young and Whittenberger suggest that airway obstruction or intercurrent pulmonary infection may contribute to the development of severe CO_2 retention. Because of the latter possibility all three of our patients were treated with penicillin although there was no clear evidence of infection.

Mechanical ventilation may relieve CO_2 retention in such patients. However, this type of treatment is not to be undertaken lightly. It requires constant nursing attendance and medical supervision. In addition serial arterial blood gas analyses and pH determinations should be done. Only by this means can assurance be given that treatment is adequate. In our experience if the CO_2 tension of arterial blood continues to remain high, there is either an inadequate airway or insufficient mechanical ventilation.

Cases I and III had the lowest oxygen saturation (excluding patients with congenital heart disease) and the most marked hypercapnia of arterial blood while breathing room air observed in this clinic since 1947. Both of these patients had predominantly pulmonary fibrosis. Presumably the respiratory insufficiency was due (1) to difficulties in diffusion across the alveolocapillary membrane and (2) to ventilatory insufficiency from long-standing emphysema and fibrosis. It is likely that intercurrent infection increased the diffusion barrier and resulted in the severe respiratory embarrassment on admission. These patients were practically moribund before being placed in a mechanical respirator. Mechanical ventilation not only blows off CO_2 but also permits oxygen therapy to relieve the severe hypoxemia. Antibiotics and

digitalis probably contributed to the success of therapy by relieving intercurrent infection and strengthening cardiac muscle.

Pulmonary hypertension develops in some patients with pulmonary emphysema and fibrosis as a result of a reduction of the pulmonary capillary bed, anoxia, secondary polycythemia and hypervolemia.[19] Recently the importance of hypercapnia has been suggested as a contributing factor in the production of pulmonary hypertension.[17] All of these conditions were pronounced in our cases on admission. Hemodynamic studies prior to therapy are available only in Case III. The mean pulmonary artery pressure was 60 mm. Hg and two and a half months later it had fallen to 29 mm. Hg. Concomitantly the $P_{a_{CO_2}}$ had declined from 77 to 48 mm. Hg and the arterial oxygen saturation had risen from 50.5 to 86.7 per cent. The arterial blood pH had become normal and the hemoglobin had declined from 18.9 to 13.4 gm. per cent. Since all the factors contributing to pulmonary hypertension were greatly alleviated before discharge from the hospital, it is not possible to delineate which was most responsible for the acute elevation of pulmonary artery pressure.

SUMMARY

1. Three patients with severe pulmonary insufficiency who developed coma following the administration of oxygen have been presented. Coma was associated with severe hypercapnia and respiratory acidosis.

2. Mechanical ventilation in the Drinker respirator resulted in recovery in two instances.

3. The course of each patient was followed by serial arterial blood gas analyses and pH determination.

4. Cardiac catheterization in one case prior to therapy revealed severe pulmonary hypertension associated with marked hypoxemia, hypercapnia and respiratory acidosis. Cardiac catheterization following treatment in each case demonstrated moderate pulmonary hypertension and increased total pulmonary resistance associated with a normal cardiac index.

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Pulmonary Hypertension in Congenital Heart Disease*

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The level of pulmonary arterial pressure in relationship to the pulmonary vascular resistance is of fundamental importance in those types of congenital heart disease which may be associated with excessive blood flow through the vessels of the lungs. Early reports of pressure in the pulmonary artery in cases of congenital heart disease provided an indefinite over-all picture of the true situation in this regard but, with greater experience, a more distinct pattern of the response in the three most common congenital defects with increased pulmonary flow has emerged.[1–4] Atrial septal defect is characterized by little increase in pressure in the pulmonary artery;[5–7] patent ductus arteriosus is characterized usually by somewhat increased pressure,[8,9] although cases in which there is a large increase in pressure have been reported.[10–11] Ventricular septal defect is characterized usually by a definite increase in pressure in the pulmonary artery while severe pulmonary hypertension is mandatory for diagnosis in the Eisenmenger syndrome.[12]

The present article is based on the critical analysis of selected data obtained by the cardiac catheterization of sixty-eight patients with atrial or ventricular septal defect or patent ductus arteriosus obtained in the cardiac catheterization laboratory of the Mayo Clinic. Its purpose is to present the essential data on blood pressure and flow in the pulmonary system, to study the incidence of pulmonary hypertension and to discuss the changes in pulmonary resistance in these conditions. The significance of differences in the incidence of pulmonary hypertension associated with atrial and ventricular septal defects is of considerable interest, because it may indicate the importance of certain factors in the control of the pulmonary circulation.

SELECTION OF MATERIAL

Because the selection of patients for cardiac catheterization varies in different institutions and because the indications for such a procedure may change in the light of increasing knowledge, it is not possible to generalize from a particular published series of cases.

Only cases in which an absolute diagnosis had been made and in which there was no evidence of cardiac failure were included in this series. Patients were referred as follows:

Atrial Septal Defect. Some of the patients with atrial septal defects seen at the Mayo Clinic are not now referred for cardiac catheterization. In general, if the patient's symptoms are not significant and if, on roentgenoscopic examination, the heart is not found to be enlarged, either no special investigations are advised or only a dye dilution curve is obtained to demonstrate presence and relative severity of pulmonary recirculation.[13] Most patients with disability or cardiac enlargement are referred for cardiac catheterization. This selection is reflected in the low incidence of uncomplicated atrial septal defect encountered in our laboratory; in only twenty-six of seventy cases in which catheterization demonstrated atrial septal defect was a diagnosis of uncomplicated atrial septal defect made. In the remaining forty-four cases an additional structural lesion was present. In the cases to be discussed the systolic pressures in the right ventricle and pulmonary artery differed by less than 10 mm. of mercury. Two of the twenty-six cases were grossly atypical on clinical grounds as both patients had been cyanotic, one from birth and the other from an early age. Some doubt still exists about the final diagnosis in these cases. In accord with common statistical practice these cases have not been included in

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the calculation of mean values but are referred to in the section on results.

Patent Ductus Arteriosus. At present patients with typical patent ductus arteriosus are referred for surgical treatment without study in the cardiac catheterization laboratory. Indications for cardiac catheterization include evidence of right ventricular enlargement, cyanosis or a non-continuous murmur; frequently such patients have higher pressures in the pulmonary arteries than are usual in this condition. However, investigations were carried out in a number of typical cases in the past and a total of twenty-four cases of patent ductus arteriosus without other anatomic anomaly were available for study.

Ventricular Septal Defect. The majority of adult patients with ventricular septal defect, or Eisenmenger's syndrome, are referred for cardiac catheterization. The patient with the classic picture of maladie de Roger, with normal electrocardiographic and roentgenologic findings is, however, least likely to be referred for cardiac catheterization. While the division into two clinical syndromes of the effects of an anatomic defect of the ventricular septum may be of considerable value in practice, there are many dynamic features which suggest that they are best considered together. It is probable that all intermediate degrees of flow patterns exist between a ventricular defect with a pure left-to-right shunt on the one hand and the classic Eisenmenger's syndrome with the shunt entirely right to left on the other. In agreement with Selzer[14] we take the view that such cases may be considered as a single group. Twenty cases of ventricular septal defect without pulmonary stenosis or other anomaly have been studied.

The selection of patients for special investigation is seldom on a random basis. The preceding paragraphs outline the limitation of our series in this respect. The clinical selection would be expected to influence the average findings toward somewhat higher pulmonary artery pressures than are truly representative of the conditions studied.

METHOD OF STUDY

Diagnostic cardiac catheterization was carried out utilizing strain-gauge manometers, cuvette and earpiece oximeters[15] and photographic recording.[16] In particular, use of the cuvette oximeter facilitated the establishment of the diagnosis because it permitted rapid sampling from different heart chambers. Direct visual reading of the oxygen saturations could be made and reported to the operator within a few seconds. It is believed that without this special instrumentation the diagnosis would not have been established with certainty in some cases.

Photokymographic records of pressure* in the pulmonary artery were obtained for the sixty-eight patients studied. Intraradial arterial pressures were recorded in all but five of the series. Mean pressures were obtained by planimetric integration of the pressure record. Usually a series of simultaneously recorded pulmonary and radial pulse complexes was measured to obtain the reported pressures. This pressure record was obtained either during or in close proximity to the period of measurement of the oxygen consumption.

Pulmonary blood flow† was calculated by the Fick principle from the oxygen consumption and the oxygen content of blood samples drawn simultaneously from pulmonary and radial arteries measured by a modification[20] of the method of Van Slyke and Neill.[21] In cases in which there was systemic desaturation the oxygen content of left atrial blood was taken to be 97 per cent of the oxygen capacity of the sample from the radial artery.

Systemic blood flow was calculated from the best available estimate of the oxygen content of

* Frequently records of pulmonary arterial pressures may be distorted owing to the generation of pressure waves by the acceleration and deceleration of the fluid mass in the catheter which accompanies the movement of the catheter in the beating heart. Such waves if unrecognized may give rise to erroneously high values for systolic pressure in the pulmonary artery. The dynamic response of the galvanometer-strain-gauge-catheter system used was within 10 per cent of static sensitivity out to a frequency of twelve cycles per second with a rapid decline in sensitivity to frequencies above this figure.[17] This type of frequency response selectively discriminates against motion artefacts which tend to be in a higher frequency range than most of the practically important components of the pulmonary artery pressure pulse.

† Even in the most experienced and careful laboratory errors within the variability of the Van Slyke method (± 0.2 vol.) may alter the calculated pulmonary blood flow by as much as 50 per cent if the arteriovenous oxygen difference is small as is the case in large arteriovenous shunts. Hence intragroup comparisons are possibly of greater significance than individual values. On theoretic grounds[18,19] estimations of blood flow by the direct Fick method may be incorrect if variations in both flow and arteriovenous oxygen difference occur during the period of measurement. Such errors would be expected to be much greater in the presence of intracardiac shunts.

mixed venous blood. In cases of patent ductus arteriosus satisfactory samples were drawn from the right ventricle. Right atrial blood was used in cases of ventricular septal defect. In atrial septal defect the average of samples drawn from superior vena cava and inferior vena cava was taken. The inadequacies of the latter estimate were recognized, but the over-all results did not appear to be remarkably in error. Both pulmonary and systemic blood flow were expressed also in relation to the surface area of the individual (pulmonary flow index; systemic flow index).

The pulmonary resistance was calculated as follows: $\frac{P_{pAm} \times 1{,}332}{F_p} = R_p$, where P_{pAm} is the mean pulmonary arterial pressure in millimeters of mercury; 1,332 is the conversion factor from millimeters of mercury to dynes per square centimeter; F_p is pulmonary blood flow in cubic centimeter per second; R_p is the total pulmonary resistance. Systemic resistance (R_s) was calculated in a similar manner: $\frac{P_{sAm} \times 1{,}332}{F_s} = R_s$. P_{sAm} is the mean systemic arterial pressure and F_s is the systemic flow. R_p and R_s are ex-

TABLE I

THE ARTERIAL PRESSURES, BLOOD FLOWS AND RESISTANCES IN THE PULMONARY AND SYSTEMIC CIRCULATIONS IN CASES OF ATRIAL SEPTAL DEFECT (A.S.D.), VENTRICULAR SEPTAL DEFECT (V.S.D.) AND PATENT DUCTUS ARTERIOSUS (P.D.A.)

Cases		A.S.D. 24	V.S.D. 20	P.D.A. 24	Significance of Differences between Means (P Values*)		
					A.S.D. and V.S.D.	A.S.D. and P.D.A.	P.D.A. and V.S.D.
Age of patient, yr.		27(3–57)	18(1–44)	22(3–46)			
Systemic pressure, mm. Hg	Systolic	117	117	129	.....	....	..
	S.D.†	15	25	22			
	Diastolic	69	66	66	.....	....	..
	S.D.	8	12	13			
	Mean	87	84	86	.....	....	..
	S.D.	10	14	13			
Pulmonary pressure, mm. Hg	Systolic	33	82	57	0.001	0.01	..
	S.D.	11	36	34			
	Diastolic	14	44	36	0.001	0.01	..
	S.D.	5	20	24			
	Mean	22	59	43	0.001	0.01	..
	S.D.	7	25	29			
Systemic, L. per min.	Flow	5.4	5.0	5.1	.....	....	..
	S.D.	1.2	2.0	1.7			
	Index‡	3.5	4.2	3.6	.....	....	..
	S.D.	1.0	1.7	1.8			
Pulmonary, L. per min.	Flow	14.8	9.7	10.8	.....	....	..
	S.D.	6.1	7.2	6.5			
	Index	9.5	7.2	7.2	.....	....	..
	S.D.	9.5	5.9	3.8			
Total resistance dynes per second per cm.$^{-5}$	Systemic	1,320	1,440	1,540	.....	....	..
	S.D.	140	470	720			
	Pulmonary	140	930	530	0.001	0.02	..
	S.D.	50	820	680			

* Differences with P values of less than 0.02 were considered to be statistically significant.
† S.D. = Standard Deviation.
‡ Index. Liters per min. per M^2.

pressed in dynes per second per cm.$^{-5}$ or resistance units (abbreviation R.U.)

RESULTS

The relevant findings in our cases are summarized in Table I. The only remarkable finding in the sex distribution was preponderance of females among the patients with atrial septal defect. In the group who were less than ten years of age were two patients with atrial septal defect, eight with ventricular septal defect and five with patent ductus arteriosus. (Fig. 1.) The systemic arterial pressure and systemic flow index were not significantly different in the three conditions.

Pulmonary Arterial Pressure. The pulmonary arterial pressure differed in the three groups. Only four of the twenty-four patients with atrial septal defect had systolic pressures in excess of 40 mm. of mercury; while thirteen of the twenty-four patients with patent ductus arteriosus and eighteen of the twenty patients with ventricular septal defect had systolic pressures greater than 40 mm. The level of 40 mm. of mercury is a useful one for comparison, for systolic pressures in excess of this value are certainly abnormal. The mean pressures in the groups have been plotted against age in the scatter diagram. (Fig. 1.) The significance of the differences between these groups was tested statistically. Systolic, mean and diastolic pressures were significantly different in the group with atrial septal defects from the other two groups. Although the systolic, mean and diastolic pressures were greater in cases of ventricular septal defect than in patent ductus arteriosus, this difference was not significant. In a number of cases the pulmonary arterial "wedge" pressure was obtained and in every instance was within normal limits.

Pulmonary Blood Flow. The pulmonary blood flow was calculated in twenty-one cases of atrial septal defect, in eighteen cases of ventricular septal defect and in twenty-two cases of patent ductus arteriosus. Because of the larger number of patients with ventricular septal defect or patent ductus arteriosus who were less than ten years of age, the results were best expressed in relation to the surface area of the individual, pulmonary flow index. It was found that the average pulmonary flow index in patients with atrial septal defect exceeded the flow in patients with either of the other conditions, but that the difference between the groups did not attain statistical significance. The average proportion of pulmonary flow representing the shunted (left-to-right) blood was between 50 and 60 per cent in all three groups, that is the pulmonary flow was about double the systemic flow.

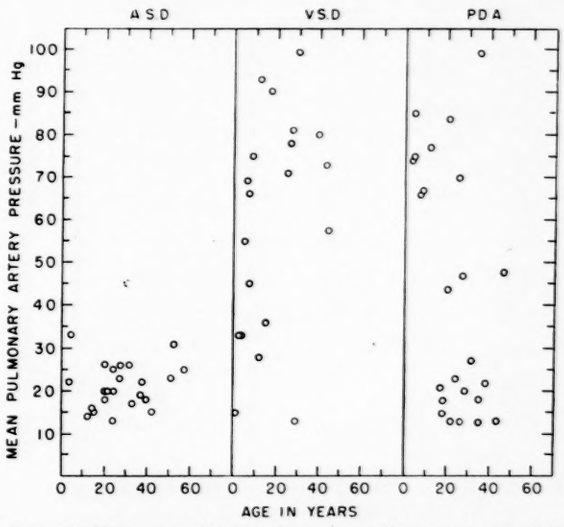

FIG. 1. The magnitude of mean pulmonary arterial pressure and the age incidence of sixty-eight patients with congenital heart disease with single defects. There are twenty-four cases of atrial septal defect (A.S.D.), twenty cases of ventricular septal defect (V.S.D.) and twenty-four cases of patent ductus arteriosus (P.D.A.). Note the similarity of age distributions and the much higher incidence of pulmonary hypertension in the groups with ventricular septal defect and patent ductus arteriosus.

In Figure 2 the mean pulmonary arterial pressure is plotted against the pulmonary flow index. There is an evident difference between the group with atrial septal defect on the one hand and the groups with patent ductus arteriosus and ventricular septal defect on the other. In spite of large shunts in the patients with atrial septal defects there was seldom any marked increase in pulmonary pressure. In patients with ventricular septal defect and to lesser extent in those with patent ductus there appears to be an inverse relationship between the pulmonary arterial pressure and pulmonary flow index, patients with the highest pulmonary arterial pressures having the lowest pulmonary blood flow.

Pulmonary Resistance. The total pulmonary resistance was calculated in those cases in which pulmonary blood flow had been measured. Normal or low values were obtained in cases of atrial

septal defects. Increased resistance was found in both ventricular septal defects and in patent ductus arteriosus; but although there was a considerable difference between the latter two conditions, this did not attain statistical significance. Both, however, were significantly different from atrial septal defects.

COMMENT

The results reported in the foregoing paragraphs allow for certain general conclusions concerning the pulmonary hemodynamics in cases of atrial and ventricular septal defects and patent ductus arteriosus. Although there is a high variability within the groups and all groups were subject to selection favoring patients with pulmonary hypertension, the number in each group is large enough to allow comparisons between the groups and the significance of any difference to be tested by statistical methods.

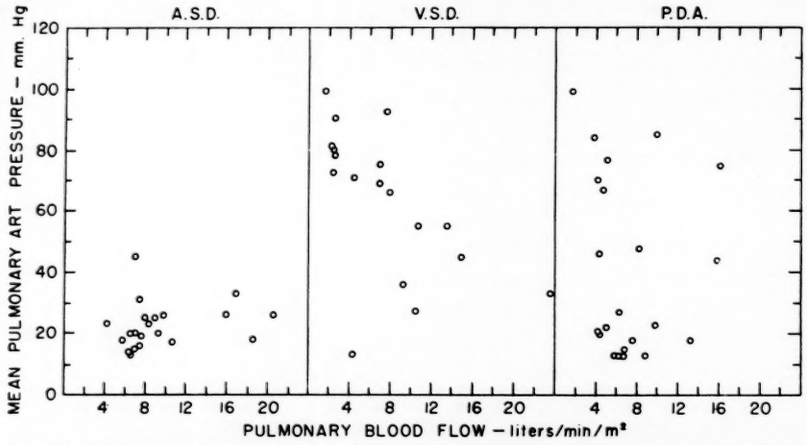

FIG. 2. The relation between the pulmonary flow index and the mean pulmonary arterial pressure in sixty-one cases. Note the contrast between patients with atrial septal defect (A.S.D.) and the other two conditions, and that in ventricular septal defect (V.S.D.) and patent ductus arteriosus (P.D.A.) the higher pressures tend to be associated with the lower flows. In reference to the accuracy of measurements of pulmonary flow in left-to-right shunts, see second footnote page 13.

In Figure 3 the total pulmonary resistance is plotted against the pulmonary flow index whereas in Figure 4 the relation between total pulmonary resistance and mean pressure in the pulmonary artery is shown. It is apparent that in cases in which the mean pulmonary arterial pressure exceeds 45 mm. of mercury, marked increases in resistance are usually associated with increases in pressure. It would not be irrelevant to point out that the two cases of suspected simple atrial septal defect with pulmonary hypertension also fall well within the pattern of the displayed data. It seems clear, therefore, that moderate pulmonary hypertension at times may apparently be related to increased pulmonary blood flow, but severe pulmonary hypertension results in the main from an increase in the resistance in the vascular bed. This increase in resistance is associated with reduction in the blood flow through the lungs in spite of the raised pulmonary arterial pressure. When increased resistance was present, this relationship was apparently independent of the location of the defect.

In the present series of cases the results indicate (1) a significant increase in pulmonary arterial pressure in the presence of ventricular septal defect and patent ductus arteriosus above the level found in cases of atrial septal defect; (2) the pulmonary flow index (pulmonary flow per square meter of body surface) did not differ significantly in any of the groups although the highest average flow was found in the patients with atrial septal defect; (3) the total pulmonary resistance was within normal limits in the group with atrial septal defect, but significantly increased in the other two groups.

FACTORS CONTROLLING PULMONARY ARTERIAL PRESSURE

The pulmonary arterial pressure is the result of the resistance at or beyond the arterial bed to the volume and velocity of the pulmonary

blood flow. In our interpretation of pulmonary hypertension we have to consider the effect of alteration of four factors:

Increase in the Resistance to Flow Beyond the Pulmonary Capillaries. This can be caused by such conditions as mitral stenosis, congestive cardiac failure and constrictive pericarditis. In such an event the pulmonary arterial "wedge" pressure is elevated. In our series of patients no signs of heart failure were present and the "wedge" pressures were within normal limits, thus an increased resistance beyond the pulmonary capillaries can be excluded.

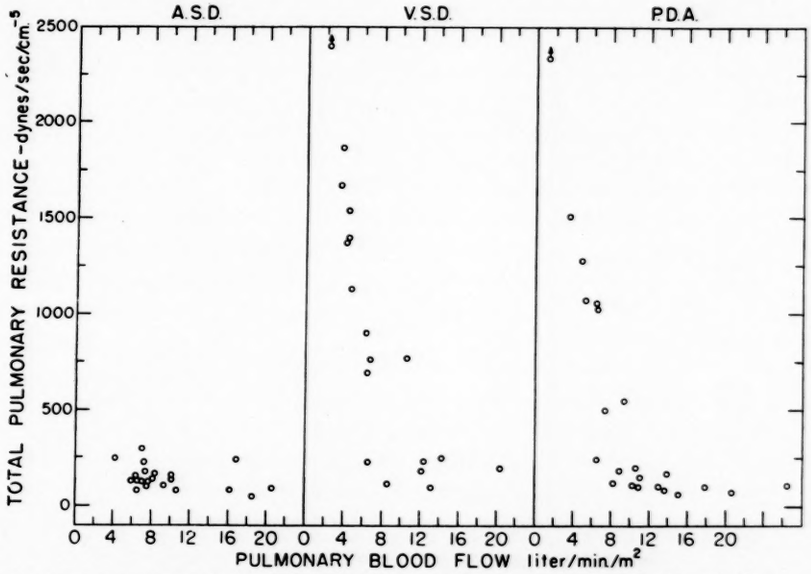

FIG. 3. The relation of total pulmonary resistance to pulmonary flow index in sixty-one cases. Note that although the distribution of flow values in the three conditions is similar the incidence of increased resistance is much higher in cases of ventricular septal defect and patent ductus arteriosus than that found in patients with atrial septal defect. The calculation of resistance involves the figure for blood flow in the pulmonary artery and, therefore, the variables are not completely independent of one another.

Increased Pulmonary Blood Flow in the Presence of Unchanged Resistance. In the normal person the total pulmonary resistance is 100 to 300 R.U. and it has been found that this value does not change with exercise when there is less than a threefold increase in cardiac output.[22–24] It logically follows that as the flow increases with exercise the resistance to that flow decreases by means of an autoregulatory mechanism. Our findings of a normal or even a decreased pulmonary resistance in atrial septal defect (average 140 R.U.; range, 49–300) agree with the earlier studies of Hickam,[6] and we may conclude that in some cases of atrial septal defect the pulmonary vessels respond to the added pulmonary flow in the same manner as to a physiologic increase in blood flow. In other cases there is a slight rise in pulmonary pressure as a consequence of the increased flow not accompanied by the "physiologic" decrease in pulmonary resistance.

Increase in the Velocity of Flow into the Pulmonary System. Recent observations on the contour of the aortic pulse indicate that the arterial pulse is a function not only of the amount of blood ejected by the heart, the run-off from the arterial system and the elasticity of the aorta, but also of the velocity of the flow and the acceleration and deceleration of the blood which occurs during its ejection into the aorta, along with other factors concerned with the physical state of the vessel.[25] As the sum of the energy components of a dynamic event remains constant, it is clear that the kinetic energy of the column of ejected blood must be accounted for; since it is probably not lost in the form of heat, it must be converted for the most part into pressure to be dissipated in the work of driving the blood through the vascular bed. In the systemic arteries it has been suggested that as much as 20 per cent of the arterial pressure may be so derived.[26] In cases

of patent ductus arteriosus and ventricular septal defect in which, in the usual circumstance, blood is being ejected through an orifice from a high pressure to a lower pressure system, these kinetic factors probably contribute heavily to the genesis of the pulmonary arterial pressure, increased elasticity resistance would be expected to result in increased systolic and pulse pressures and lowered diastolic pressure but not to alter mean pressure values. Of more importance in regard to the subject of this paper, in the presence of a high elasticity resistance, the kinetic

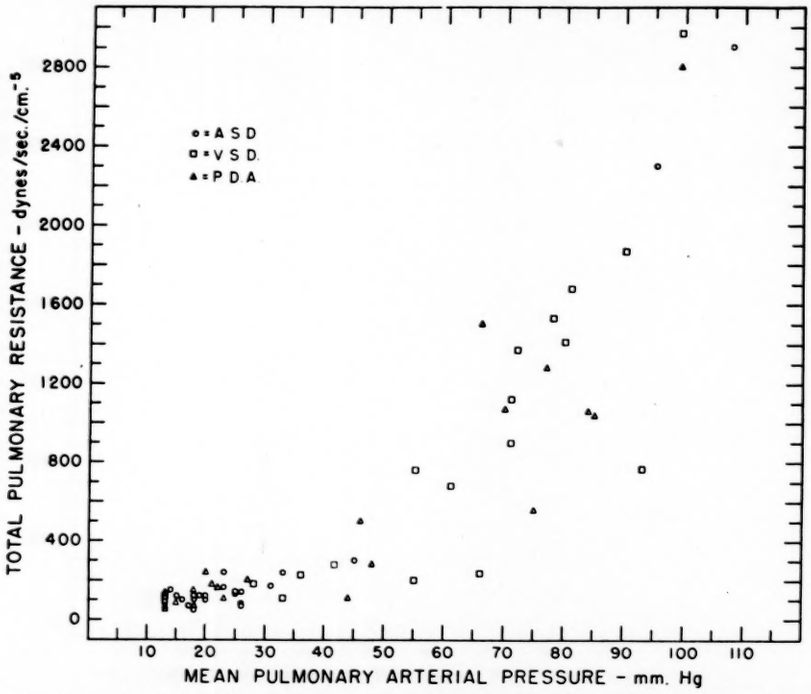

FIG. 4. The relation of total pulmonary resistance to mean pulmonary arterial pressure in sixty-three cases of congenital heart disease. The two additional cases of atrial septal defect (A.S.D.) with gross pulmonary hypertension are included in this figure. As in Figure 3, these variables are partially dependent on one another. Note that the pulmonary resistance is increased (>250 R.U.) in any instance in which the mean blood pressure in the pulmonary artery exceeds 50 mm. Hg, and that this increase appears to be independent of the nature of the lesion.

and may be responsible for the difference between these two conditions and atrial septal defect in which such kinetic effects are more nearly normal. The concept of "elasticity resistance" has been recently introduced in regard to the pulmonary circulation.[27] The equation $E = \frac{\Delta P}{\Delta V}$ (E = the effective volume elasticity coefficient) is an inverse expression of the arterial capacity in relation to the pressure under which blood enters it. E, so defined is not a constant, but will vary with the physical characteristics of the vessel wall pertaining to the degree of distention of the vessel. Hence isolated values of E, unrelated to a definite level of pressure cannot be used as a comparative index of elasticity. An energy of the ejected blood would be dissipated to a lesser extent in the distention of the large pulmonary vessels and to a greater extent in the smaller ones.

Increased Pulmonary Resistance or a Greater Degree of Obstruction to the Flow of Blood Through the Small Pulmonary Vessels. Our calculations of resistance are based on measurements of pressure and flow, and the finding of increased resistance means that the observed increase in pulmonary arterial pressure is disproportionately greater than the increase in pulmonary blood flow. These relative alterations in flow and pressure can best be quantified in terms of resistance. Our findings indicate that mean pulmonary arterial pressures in excess of 50 mm. of mercury

are associated with a calculated pulmonary resistance above the normal range. In ventricular septal defect (average 930 R.U.; range 100–3,000), and in patent ductus arteriosus (average 530; range 87–2,800) elevated pulmonary resistance was the usual finding but values of pulmonary resistance within the range of normal were found in both groups. This increase in resistance must be proximal to the pulmonary capillaries. The nature of the pulmonary resistance will be discussed in a later section of this paper.

The importance of pulmonary resistance may be demonstrated by consideration of the major difference of atrial septal defect from ventricular septal defect. Clearly, the most extreme degrees of septal defect are seen in cases of single atrium and single ventricle. While the former condition (cor triloculare biventriculum) is relatively well tolerated,[28] survival in the latter condition (cor triloculare biatrium) is possible only when there is high pulmonary resistance and, as a result, a marked degree of pulmonary hypertension, for in the absence of such a state by far the greater part of the ventricular output would flow into the pulmonary capillaries under high pressure and produce fatal vascular damage. It is unnecessary to point to the failure of systemic flow which would result also. Although morbidity is high and survival is usually short in this condition, it is clear that high pulmonary resistance must exist from birth in this condition to allow survival of any individuals. Dexter and associates[29] considered the Eisenmenger complex as an example of a physiologically common ventricle and indeed it is possible to extend this concept to include many cases of ventricular septal defect and rare cases of patent ductus.

The persistence of pulmonary resistance of sufficient magnitude to prevent flooding of the lungs, and to provide adequate flow of blood to the systemic circulation appears mandatory for the continuance of life in patients with moderate or large defects of the ventricular septum and also in some cases of patent ductus arteriosus. The objective evidence for this premise is not yet great but a relationship between the circulatory disturbance and the size of ventricular defects may be suggested. At necropsy hearts with large defects were found characterized by marked hypertrophy of the right ventricle and severe obstructive changes in the pulmonary arteries and arterioles.[30] A short wide ductus was found on surgical exploration only in those of our cases of patent ductus arteriosus in which cardiac catheterization had revealed significant pulmonary hypertension.

It does not follow, however, that in a given case the pulmonary resistance is fixed and change does not occur. Indeed, the contrary is probably true, and in many cases the pulmonary resistance does increase with a resultant fall in pulmonary blood flow and the development of a right-to-left shunt. However, some patients with patent ductus seem to have had pulmonary hypertension at an early age as, at death, the left ventricle has been of normal size. The implication is that equivalent pulmonary and systemic resistance existed during life. Fundamentally, in these conditions, the pulmonary hypertension is an indispensable component of the balance between pulmonary and systemic arterial systems and, if critically maintained, may be compatible with a degree of cardiac efficiency surprising in relation to the severity of the anatomic defect. Often, however, this is not the case and the inexorable increase in pulmonary resistance can result only in a fatal outcome for the patient.

To this point the discussion has been of a teleologic nature. The exact cause of increased pulmonary resistance is an enigma and is likely to remain so until long-term studies are undertaken from birth onward. However, speculation is justifiable; at least three mechanisms may play a part individually or in combination to produce the aforementioned increase in pulmonary resistance.

Increased Pulmonary Resistance in Primitive Type of Pulmonary Vessels. There may be persistence of the fetal structure of pulmonary arteries and arterioles.[31] The blood flow to the lower part of the fetus passes chiefly from the right ventricle to the aorta by way of a patent ductus arteriosus,[32] and there is little or moderate blood flow through the small pulmonary arteries. Civin and Edwards[33] traced the development of the pulmonary arteries and arterioles in a series of sections obtained at necropsy from fetuses, infants, young children and adults. In the muscular fetal arteries the lumen of the vessel is less than the transverse diameter of the vessel wall. Only between the second half of the first month and the sixth month of postnatal life is this relationship reversed to conform to the adult pattern. This increase in cross sectional diameter of the lumen of pulmonary vessels may be paralleled by a progressive decline in pulmonary resistance and,

thus, in pulmonary arterial pressure. To complete this process may take days, weeks or even months. Persistence of the fetal type of vessel would maintain the pulmonary resistance in congenital anomalies in which there is the possibility of flooding of the pulmonary arterial bed from a high pressure site. Edwards and associates have taken this beyond the stage of conjecture and demonstrated that muscular arteries of the fetal type may be found in the Eisenmenger complex[34] and in other anomalies.[35,36] The important question remaining is in the cause of the persistence of the thick muscular media of these vessels or, conversely, the cause for the fundamental structural change that these vessels undergo in the normal infant. The mechanism underlying the persistence of the fetal type of vessels in the pulmonary system in cases of congenital heart disease is a process fundamental to the problem of pulmonary hypertension.

Degenerative Pulmonary Vascular Disease. Intimal hypertrophy and degeneration, atherosclerosis and arteriosclerosis and the formation of occlusive thrombotic lesions may decrease the functional cross sectional area of the pulmonary vascular bed and thus cause a rise in pulmonary arterial pressure. Pulmonary arteritis and pulmonary arteriosclerotic changes have been reported in certain anomalies.[37,38] Such lesions might not be expected in younger patients but the kinetic effects of the type of pressure pulse associated with some cases of ventricular septal defect or of patent ductus arteriosus may cause structural changes in the walls of the pulmonary vessels. If these changes are associated with a decreased distensibility or increased elasticity resistance of the main pulmonary vessels, the pressure pulse, including components resulting from acceleration and deceleration of blood at the defect, will be transmitted more readily to the small pulmonary vessels and, hence, may promote degenerative changes in these vessels. The presence of such structural changes alone is not sufficient to explain the increased pulmonary resistance which must have existed from birth. They may, however, explain the progressive changes in circulatory dynamics which probably occur in many cases of ventricular septal defect and in some cases of patent ductus arteriosus. Kinetic effects of the same magnitude would not pertain to the pressure pulse in cases of atrial septal defect in which, apart from volume considerations, the dynamics of right ventricular ejection is probably normal. In its early genesis the rare occurrence of pulmonary hypertension in atrial septal defect may be associated with extremely large pulmonary flow, which would necessitate departure from the normal right ventricular ejection pattern possibly resulting in kinetic factors similar in magnitude to those postulated in cases of ventricular septal defect and patent ductus arteriosus.

Reflex Vasospasm of the Muscular Pulmonary Vessels. At present there is insufficient evidence to estimate what part, if any, reflex vasoconstriction may play in the magnitude of the pulmonary resistance in congenital heart disease. Acute pulmonary embolism[39] and anoxia[40,41] cause an increase in pulmonary pressure. Inhalation of 100 per cent oxygen has been found to reduce the level of pulmonary hypertension in a number of cases of congenital heart disease[42] and to alter the magnitude or even change the direction of the shunt through a patent ductus arteriosus[43] or an atrial septal defect.[44] The use of adrenergic and ganglionic blocking agents should provide a useful investigative tool in this field.

The treatment of pulmonary hypertension in congenital heart disease is not the purpose of this paper. It is of interest, however, that attempts are being made in the Eisenmenger complex to create pulmonary stenosis,[45] in order to prevent vascular damage and the development of occlusive changes in the pulmonary vessels. As the dimensions of the stenotic pulmonary artery are critical in determining the magnitude of the shunt and volume of flow, it appears better to us to direct efforts to the development of a technic to permit closure of the defect early in life, presumably to allow for the resolution of the fetal type of medial hypertrophy and to eliminate the characteristics of the pulmonary arterial pressure pulse and excessive pulmonary blood flow supposedly conducive to the development of occlusive degenerative changes thereon.

SUMMARY

With the aid of the cardiac catheterization technic a study has been made of the incidence and severity of pulmonary hypertension in a selected group of patients with single cardiac anomalies; twenty-four cases of atrial septal defect, twenty-four cases of patent ductus arteriosus

and twenty cases of ventricular septal defect. For all these patients, none of whom were in congestive failure, the diagnosis had been made with a high degree of certainty.

Although pulmonary blood flow was not significantly different in the three groups, a mean pressure in the pulmonary artery of more than 40 mm. of mercury was observed in only one case of atrial septal defect, but occurred in fourteen of the cases of ventricular septal defect and in ten of patent ductus arteriosus. Severe hypertension was also found in two additional atypical cases of atrial septal defect. When moderate or severe pulmonary hypertension was present, it was due to increased pulmonary resistance as the pulmonary blood flow usually was decreased or within the range of normal. The available data establish, but do not permit a complete explanation of, the differences in pulmonary resistance between the group of patients with atrial septal defect and the groups with ventricular septal defect and patent ductus arteriosus.

Maintenance of a high pulmonary resistance is essential for survival in many cases of ventricular septal defect and patent ductus arteriosus. This increased resistance may be due in part at least to a persistence of the fetal structure in the small pulmonary arteries and arterioles, the cause of which is, however, unknown.

The development of compensatory vascular changes to reduce excessive pulmonary blood flow and the development of degenerative vascular changes may be caused by increased pulmonary flow. But, since the level of pulmonary blood flow was not significantly different among the three groups studied, the volume of flow alone cannot account for the development of the changes in pulmonary resistance found. It is suggested that factors of kinetic energy involved in the ejection of large volumes of blood from a high to a low pressure system such as occurs in many cases of ventricular septal defect and patent ductus arteriosus contribute important components to the pulmonary pressure pulse in these conditions, that are not present in the pulmonary pulse associated with the usual cases of atrial septal defect, in which the right ventricular ejection pattern is essentially normal. Such kinetic energy factors may contribute to the differences in calculated resistances in the pulmonary bed which have been obtained and may be conducive to degenerative occlusive changes in the pulmonary arterioles.

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Complete Anomalous Pulmonary Venous Drainage*

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IN 1739 the first description of anomalous pulmonary vein drainage into the superior vena cava was mentioned and attributed to Winslow.[1] It was not until 1868 that total pulmonary venous drainage into the right side of the heart without associated major cardiac defects was described as a pathologic entity.[2] From then until the time of Brody's publication[3] in 1942 sporadic cases were reported in many countries. In Maude Abbott's series[4] of 1,000 cases of congenital heart disease there were four with anomalous pulmonary venous drainage, but three of these were complicated anomalies. The current interest in congenital heart disease spurred on by the widening surgical possibilities has led to numerous papers on the subject in the last fifteen years.[5–18] While this is not a common defect, neither is it a rare one. Several authors have been able to collect two to four cases. In the city of Toronto Heart Registry, MacLean[20] found two cases in 1952 among 300 cases of congenital heart disease between birth and fifteen years.

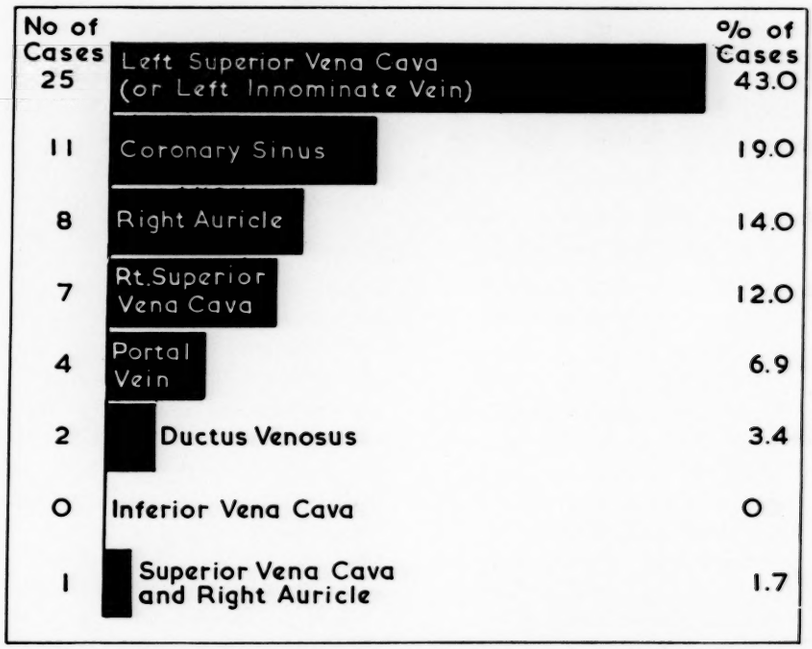

FIG. 1. Site of anomalous pulmonary venous drainage in fifty-eight autopsied cases.

Partial pulmonary venous drainage into the right auricle or its tributaries usually occurs without inconvenience to the individual and is not uncommon. Smith[9] reports seventy-five such cases from culling the literature. These cases do not constitute a medical problem as a rule. Signs and symptoms are always produced,

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however, when there is complete drainage of all the pulmonary veins into the right auricle or its tributaries. It is the purpose of this paper to deal with this latter group in which the drainage is total and uncomplicated and not with the less clinically significant group in which the drainage is partial. We have data on fourteen such cases, thirteen of them examined at postmortem.

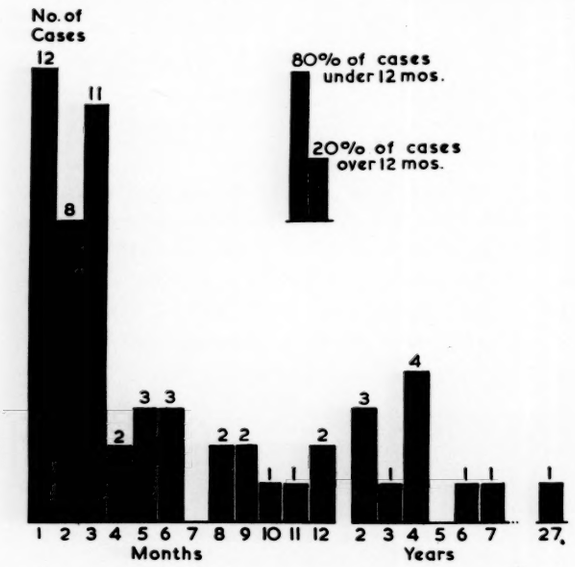


FIG. 2. Complete anomalous pulmonary venous drainage; age at death in fifty-eight autopsied cases.

PATHOLOGY

A review of the literature indicates some variation among different authors in the nomenclature for the site of abnormal venous drainage. Those that drain into a left superior vena cava or a left innominate vein should probably be considered together since they are one and the same condition, and it is a question of terminology rather than anatomical variation.

A review of forty-five proven cases culled from the literature plus our own thirteen gives a total of fifty-eight. These have been divided according to their site of anomalous drainage and the order of frequency is shown in Figure 1.

In the several publications on the subject the ages have ranged from eight days to twenty-seven years. In the younger age groups the diagnosis was usually not made until postmortem was carried out. In the current literature the patients in whom the diagnosis was made during life have usually been between five and twenty-one years of age. It seems now, with a better understanding of this anomaly and of its clinical findings, the diagnosis should be made very early in life. The mortality figures show that the majority of these patients do not survive the first year of life. The ages at death in the fifty-eight postmortem cases are shown in Figure 2. It will be seen that 80 per cent of the cases have died in the first twelve months and the vast majority of these have been in the first, second or third months. A few have survived the first decade of life and one case has been seen in the twenties. It is rather remarkable to note that of two patients with the same anomaly one may die in the first week of life and the other may survive two decades. In all probability the chief factor favoring survival is the size of the opening of the foramen ovale which, if large, permits a sufficient flow of blood to the systemic circulation, thus relieving the load on the right heart to some extent.

The anomalous pulmonary veins drain into a common trunk which appears like a widened vessel and is not in any way comparable in size to a normal left auricle. There were five distinct exceptions to this in fifty-eight cases; three cases had pulmonary veins draining into the coronary sinus via four separate channels and two cases had drainage into the right auricle in the same manner. In the majority of cases, however, the blood is carried from the collecting sinus-like structure into a common vein which communicates directly or indirectly with the right side of the heart. The right auricle thus must accept all the venous blood from the systemic as well as the pulmonary veins. This raises the right auricular pressure and the foramen ovale is kept open. The mixture of the cyanotic and oxygenated blood then reaches the left auricle, left ventricle and systemic vessels and the pulmonary arteries via the right ventricle.

The pathologic effect of this anomalous condition is to enlarge greatly the right auricle and the right ventricle while the left auricle and the left ventricle are consequently underdeveloped. The measurements of these various chambers and vessels are shown in Table 1. The right auricle is five to ten times as large as the left auricular cavity. The right ventricular cavity is three to five times as large as the left ventricular cavity. However, the thickness of the walls of the two ventricles is usually very similar. The common pulmonary vein is approximately the same diameter as the right superior vena cava except for a few instances in which the latter was distinctly larger.

TABLE I

COMPARATIVE SIZE OF VESSELS AND CHAMBERS IN THIRTEEN AUTOPSIED CASES WITH TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE (HOSPITAL FOR SICK CHILDREN, TORONTO)

Case No.	Age	Drainage of Pulmonary Veins	Ductus Arteriosus	P.F.O.	Estimated Comparative Size of (mm.)				Maximum Thickness (mm.)			Diameter (mm.)			Size of A-V Valves		Internal Circumference (mm.)	
					R.A.	L.A.	R.V.	L.V.	R.V.	L.V.	S	Common Pulmonary Vein	R.S.V.C.	Waist of L.A. Appendage	Tricuspid	Mitral	Aorta	Pulmonary Artery
				mm.											Admit			
1. S. V.	9 wk.	L.S.V.C.	Closed	Probe patent	5–6	1	4	1	8	7	10	6	8	6	Little finger	No finger	18	22
2. B. H.	19 days	R.S.V.C.	Patent	6 × 3	4–5	1	3	1	4	5	9	4	8	6	Little finger	No finger	20	22
3. M. W.	2 mo.	R.A.	Patent	3 × 3	8–10	1	. . .	. . .	7	5	4	0	7	6–7	Index	No finger	20	22
4. S. W.	11 mo.	L.S.V.C.	Closed	PFO-4 × 2 ASD-2 × 2	10	1	5	1	5–6	6–7	7	12	16	5–6	2 Fingers	No finger	25?	40
5. L. C.	11½ mo.	L.S.V.C.	Closed	ASD-15 × 6	4–5	1	5–6	1	8–9	7	7	9	12	7	2 Fingers	No finger	23	32
6. P. R.	3½ yr.	L.S.V.C.	Closed	ASD-15 × 10	5	1	3	1	5	8	9	14	15	4–6	3 Fingers	Index	23	45
7. B. P.	7¼ yr.	L.S.V.C.	Closed	ASD-10 × 10	5	1	3	1	13	12	14	14	20	10	3 Fingers	Index	45	70
9. B. L.	8 days	L.S.V.C.	Patent	3 × 2	4–5	1	3	1	8	6	6	NK	8	8	Little finger	No finger	15	25
10. G. C.	3 wk.	L.S.V.C.	Patent	Patent	NK	NK	NK	NK	NK	NK	NK	6	9	NK	NK	NK	NK	NK
11. K. D.	8 wk.	L.S.V.C.	Probe patent	6 × 3	5	1	4–5	1	5	7	6	6	7	5	Little finger	No finger	18	25
12. M. B.	3 mo.	Cor. sinus	Closed	10 × 2	8–10	1	3	1	6	6	6–7	8–9	5	5–6	Index	No finger	25	27
13. J. O.	21 days	Portal vein	Patent	ASD-3 × 2	NK	NK	NK	NK	4	NK	NK	4–8	NK	NK	NK	NK	NK	NK
14. M. I.	8½ mo.	L.S.V.C.	Closed	10 × 6	5	1	3	1	8	8–9	7	15	18	8	Index	Index	27	40

P.F.O. = Patent foramen ovale
R.A. = Right auricle
L.A. = Left auricle
L.S.V.C. = Left superior vena cava
R.S.V.C. = Right superior vena cava
R.V. = Right ventricle
L.V. = Left ventricle
S = Septum
NK = Not known

The mitral valve opening was invariably smaller than that of the tricuspid valve, an indication of the difference of blood flow between the two orifices. In about half of the cases the pulmonary artery was the same size as the aorta. In the other half the pulmonary artery was at least a third as large again as the aorta.

There were two cases of the eleven that showed intermittent cyanosis before failure occurred. In one of these crying brought a slightly dusky color to the lips and in the other feeding produced moderate cyanosis.

There were three children who survived the first year of life and one of these, a seven year old girl, had frank cyanosis. The saturation of oxygen in her arterial blood was 63 per cent. The other two had no visible cyanosis present at rest or with exercise and had arterial oxygen saturations of 88 per cent and 90 per cent, respectively. Thus considering the whole group, cyanosis was not a common clinical feature at rest or with activity. In a few cyanosis was evident with crying or with exercise but in the rest there was insufficient drop in the oxygen saturation of the blood to produce clinical cyanosis.

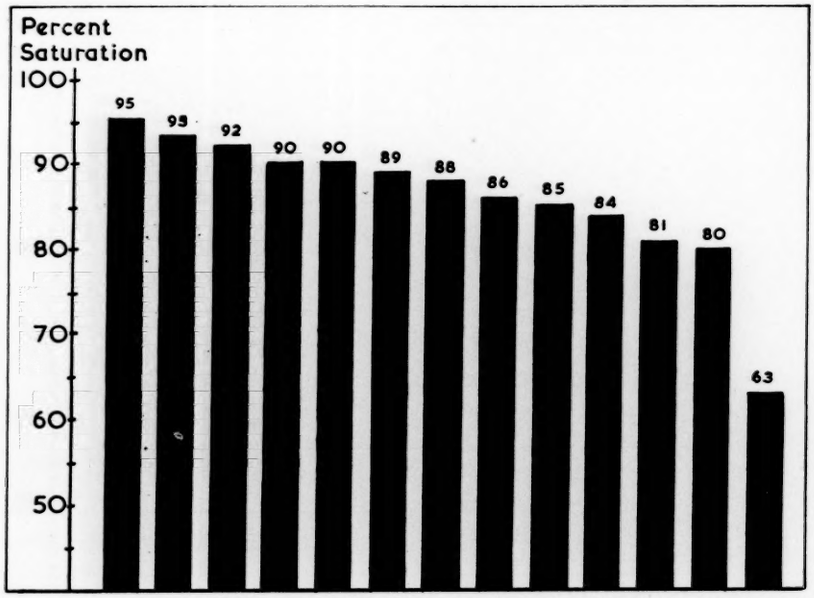


FIG. 3. Arterial oxygen saturation in thirteen cases of complete anomalous pulmonary venous drainage. The percentage oxygen saturation was derived from Van Slyke analysis of systemic arterial blood. It may be seen that the majority of values lie in the range where clinical cyanosis would not be appreciated.

Since the left auricular appendage has been used as an anastomotic channel with the anomalous vessel in an effort to route the blood into the left auricle, it is of considerable interest to measure the waist of this structure and to compare its diameter with that of the anomalous vein. In Table I it will be seen that the waist of the left auricular appendage is usually smaller than that of the anomalous vein.

CLINICAL FEATURES AND ACCESSORY INVESTIGATIONS

Cyanosis. Cyanosis is not a significant feature in most of these children in spite of the fact that there is mixing of the systemic and pulmonary venous blood in the right auricle. (Fig. 3.) None of our cases were observed to be cyanotic in the first few days of life (there was one exception to this: Case 3 was cyanotic for a few hours after birth and then appeared a normal color). All cases were cyanotic terminally.

There were eleven babies who died in the first year of life and cyanosis was a feature only in the terminal stages when heart failure supervened.

Heart Murmurs. Observations on the heart murmurs were available in thirteen of the fourteen cases. In three instances no murmurs were audible at all. These were infants under three months of age and, since eleven of our cases may be classed as infants, our impression is that one-third of this age group had no murmur.

A murmur was present in ten of thirteen cases. The murmur most commonly heard was short and systolic in time, of very moderate intensity, between the second and fourth left interspaces

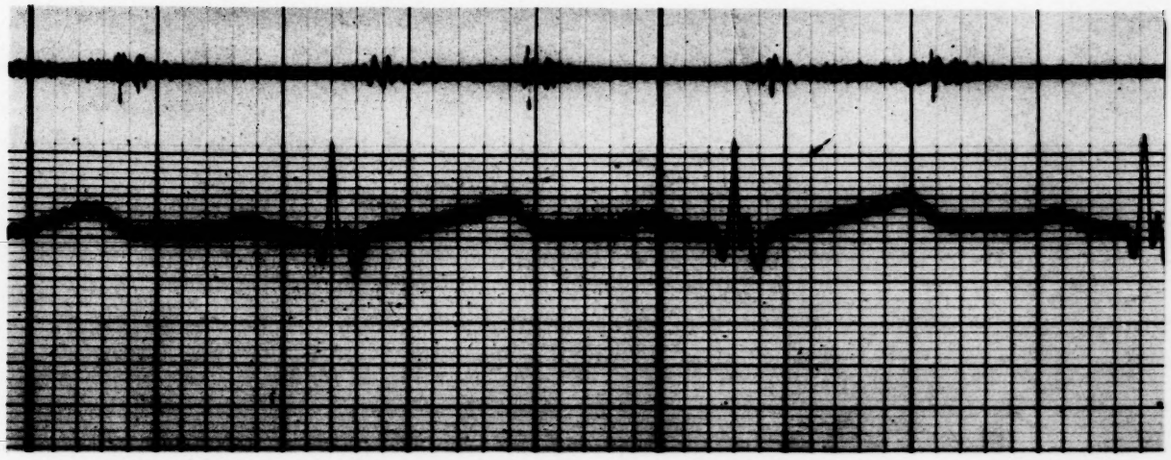
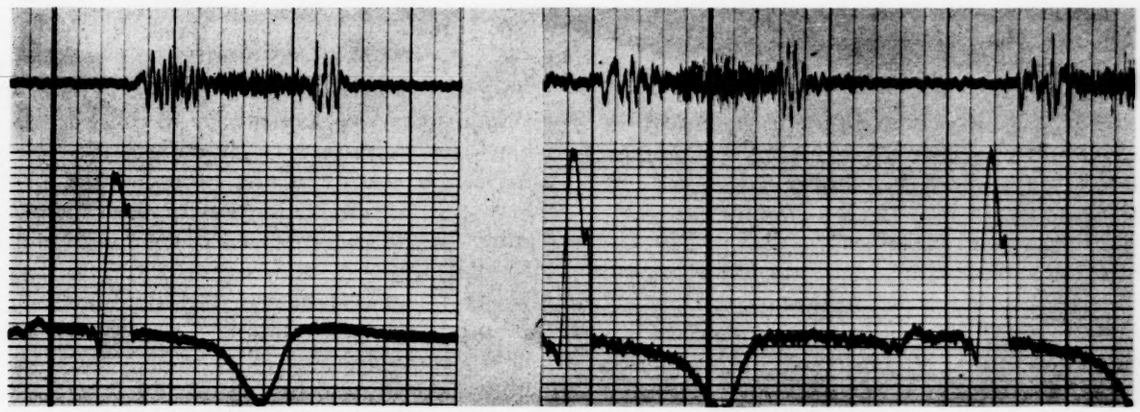


FIG. 4. Case 6, P. R., age three and one-half years. Phonocardiogram from pulmonary area in boy with all pulmonary veins entering a left superior vena cava.



Deep Expiration Deep Inspiration

FIG. 5. Patient B. P., female, age seven years. Phonocardiogram recorded over the xiphisternum, showing a distinct systolic murmur maximum in this area and a less distinct diastolic murmur. It was thought these were possibly of tricuspid origin and support was given to this by their accentuation on deep inspiration.

near the sternum. This type was recorded in nine cases. Four of the nine also had a diastolic murmur in the fourth left interspace between the apex and the sternum.

On examining Case 6, a boy three and one-half years of age, one of us noted a soft continuous murmur in the pulmonary area. It had the usual quality of a venous hum but it was present not only in the pulmonary area but also part way down the left border of the sternum. A phonocardiogram of this murmur is shown in Figure 4. A similar murmur was subsequently heard in three additional children, making four all told. In one instance it was heard in a six weeks old baby. In all four the abnormal pulmonary venous drainage was into the left innominate vein. Since the murmur was heard over this area, it was considered highly probable that it was due to turbulence set up by the large abnormal blood flow as it entered the left innominate vein. Thus of the nine cases with this particular site of venous anomaly, four had a continuous murmur in the pulmonary area. It should be emphasized that this venous hum may be inconstant. In Case 1 it was heard only after repeated examinations. It need not be confused with patent ductus arteriosus since it is softer and shows no marked variations in systole and diastole. The systolic murmur between the apex and the sternum may have been due to tricuspid insufficiency since there was accentuation with deep inspiration. (Fig. 5.) Certainly with the tremendous dilation of the right auricle and ventricle one would expect some degree of insufficiency.

X-ray and Fluoroscopy. The radiologic exami-

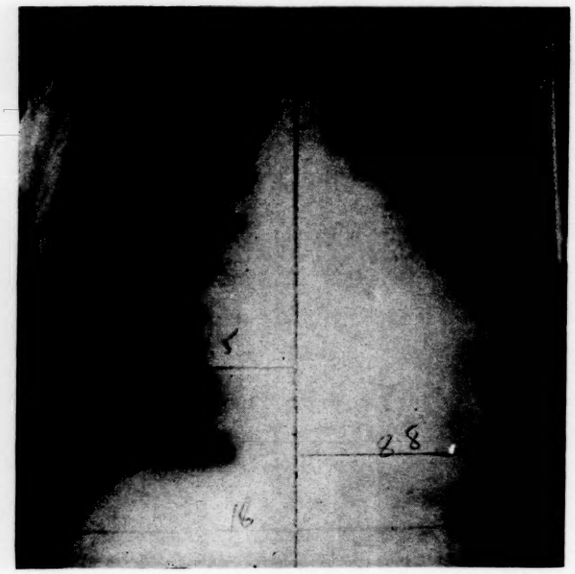


FIG. 6. X-ray of Case 7 showing typical supracardiac shadow at five years of age.

nation of the heart is most useful in making a diagnosis in this type of anomaly. This is particularly true among the children whose pulmonary veins drain into the left innominate vein. Here there is a characteristic shadow in the x-ray, an example of which is shown in Figure 6. There is revealed a heart that is moderately enlarged. The hilar shadows were markedly increased and under the fluoroscope they could be seen to pulsate. The pathognomonic shadow is that of a wide, quietly pulsatile arc seen on either side of the supracardiac area in the anterior mediastinum. It has the appearance of a mediastinal moustache and has been described by Snellen and Albers[16] as forming a figure of eight with the rest of the heart. Such a shadow is now realized to be diagnostic of all the pulmonary veins draining into the left innominate vein and is shown in the cases reported in the literature in which x-rays were exhibited in children. The diagrammatic outlines of the heart shadows in our Cases 4, 6, 7, 8 and 14 are shown in Figure 7 and reveal this typical shadow.

Usually this diagnostic shadow fails to show up in the first few months of life. We have had four cases with x-rays in this age group; outlines of these hearts are shown in Figure 7. In none of these is the supracardiac shadow present. They do, however, show enlargement of the heart and increased hilar shadowing. Our youngest case with the typical supracardiac venous shadow was five and one-half months (Case 14) but one infant reported, aged nine weeks, had the fully developed radiologic picture.[15]

There have been a few published x-rays of patients whose anomalous pulmonary venous drainage is into the right superior vena cava, right auricle, coronary sinus or inferior vena cava. Those available have been traced and are recorded in the lower half of Figure 7. Anomalous pulmonary venous drainage into the right auricle was present in one of our cases. The outline of the heart is shown in Figure 7 along with the outline of the heart reported by Winter et al.[10] It will be seen that there is enlargement of the heart in both cases and there is a somewhat similar outline. The shadow is not diagnostic where pulmonary veins enter the right superior vena cava and the one clue that one may get from the x-ray is the somewhat broadened shadow of the superior vena cava on the right. (Fig. 7.)

Pulmonary veins entering the coronary sinus produce a shadow very similar to that recorded when the pulmonary veins enter the right auricle. An outline of the x-rays of the heart when this anomaly is present is shown in Figure 7. This picture is not pathognomonic although three of the x-rays are sufficiently alike to make one suspect the diagnosis when the other clinical findings are taken into consideration.

One feature which may at times prove of diagnostic value is shown in Case 1 (Fig. 7) in which progressive enlargement of the heart is shown over the first two months of life.

Angiocardiography may occasionally be of distinct value in making the diagnosis. Several authors have demonstrated an anomalous vein entering the inferior vena cava from the right lung.[12,16] Albers and Snellen also demonstrated by angiocardiography an anomalous vessel high up on the left, entering the left innominate vein. However, in children over one year of age this anomalous vein can usually be seen quite clearly in an ordinary x-ray of the chest. Angiocardiography might be of some value in the early months of life when the x-ray and fluoroscopy does not show this typical shadow. On the whole, however, this technic does not give as much aid in diagnosis as other investigative procedures and has in practically all the reported instances uncovered cases only with partial pulmonary venous anomalies.

Cardiac Catheterization. When an anomalous

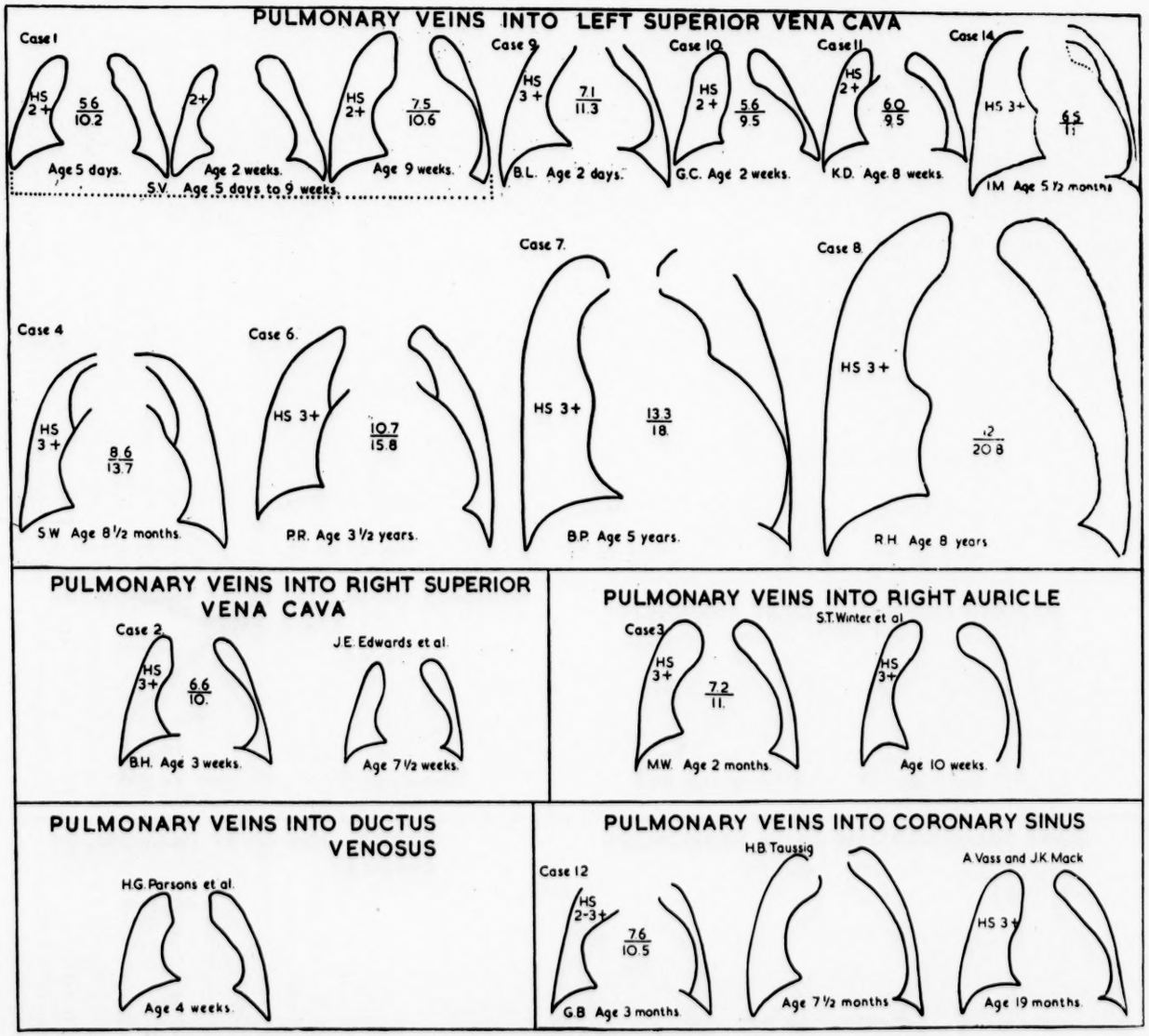


FIG. 7. Cardiac contours in various types of total anomalous pulmonary venous drainage.

pulmonary venous return is suspected cardiac catheterization is a very important step in narrowing down the diagnostic possibilities. If the oxygen content is raised in the superior vena cava, one could be dealing with pulmonary veins draining into a left innominate vein or into the superior vena cava. If the oxygen content is raised in the inferior vena cava, one could be dealing with pulmonary veins entering the portal vein, ductus venosus or into the inferior vena cava itself. If the oxygen content is raised in the right auricle only, then one could be dealing with pulmonary veins entering the right auricle or pulmonary veins into the coronary sinus, or a patent auricular septum. Less common causes of a rise of oxygen content in the right auricle or great veins are systemic arteriovenous fistulas, a ventricular septal defect with tricuspid insufficiency and a sinus of Valsalva ruptured into the right auricle.

The literature contains full reports of cardiac catheterization studies on nine cases of total anomalous pulmonary venous drainage.[11,13–16] These data are tabulated in Table II along with the findings of our own four cases. We have not included a number of reports with suggestive but insufficient data to show that the anomaly is a total one.

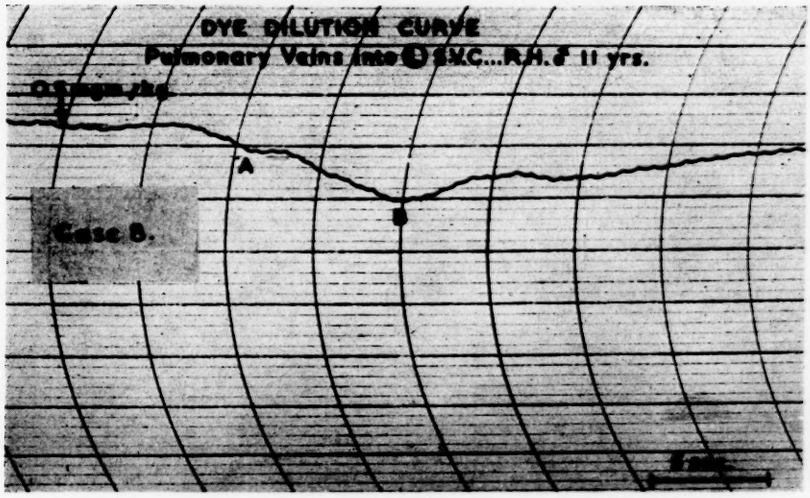
The outstanding finding at cardiac catheterization is the presence of a high oxygen content of the blood in the right auricle, which value nearly always approximates that of a systemic artery. When the anomalous trunk enters a tributary of the inferior vena cava, sampling should reveal the characteristic rise in oxygen content in the latter situation. When the pulmonary veins enter the innominate vein by a left superior vena cava, a high oxygen content is always found in blood in the right superior vena cava and in the innominate vein. When the pulmonary venous drainage occurs separately into the right auricle or via the coronary sinus, the catheter findings are less specific. While a pulmonary vein may be entered from the right auricle in the former case, thus demonstrating pathologic anatomy, in the latter circumstance it is often impossible to demonstrate anything more than a marked rise in oxygen content of the blood in the right auricle. Direct passage of the catheter from the right auricle into a pulmonary vein, especially on the right side, should be interpreted with great caution. It is

TABLE II

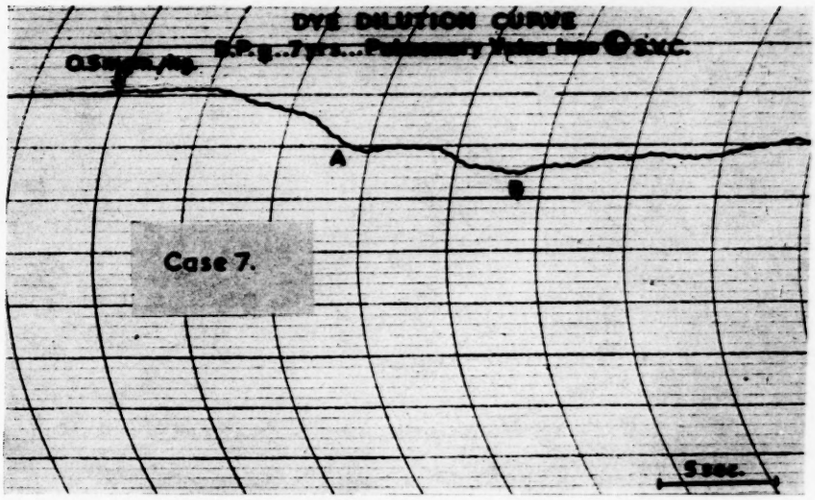
SUMMARY OF DATA FROM CARDIAC CATHETERIZATION IN TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE REPORTED IN THE LITERATURE TOGETHER WITH FOUR CASES FROM THE HOSPITAL FOR SICK CHILDREN, TORONTO

Author	Age	Sex	Oxygen Content, Vol. % or % Saturation							Pressure in mm. Hg			
			I.V.C.	S.V.C.	R.A.	R.V.	P.A.	Systemic Artery	Capacity	Systemic Artery	R.A.	R.V.	P.A.
Freidlich et al	4 yr.	F	....	15.7	16.5	16.6	....	16.5	18.4	.....	22/18	126/6	.....
	2 yr.	M	10.1	14.0	14.7	13.4	13.8	13.6	16.9	.....	.....	78/2	.....
Grishman et al	25 yr.	M	....	18.3	17.5	....	....	18.8	19.6	.....	.....	.....	.....
Johnson and McRae	11 yr.	M	12.4	15.1	18.3 15.8	15.4	15.3	14.1	16.5	.....	12	28	20
Parsons et al	6 yr.	F	....	98	13.8 95	95	....	....	100	.....	.....	81/41	73/43
Snellen and Albers	5 yr.	M	76	87	85	83	87	81	100	.....	.....	68/9	60/11
	7 yr.	M	....	85	....	73	68	86	100	.....	.....	.....	.....
	20 yr.	M	73	75 95	84	88	88	89	100	128/68	.....	105/0	55/15
	22 yr.	F	73	92 98	94	91	94	93	100	110/70	.....	50/−1	28/15
Keith et al. Case 4	10 mo.	F	8.4	12.7	12.5	....	....	13.8	16.4	160/110	.....	185/0	.....
Case 14	5½ mo.	F	6.6	11.6	14.1	11.4	....	13.6	14.7	108/66	10/0	62/0	.....
Case 6	3¾ yr.	M	10.1	13.1	12.6	11.1 12.6	12.9	13.3	15.0	135/60	.....	.....	.....
Case 7	4 yr.	F	12.2	18.4	16.2	14.9	....	14.3	22.6	90/30	12/5	55/0	.....

I.V.C. = Inferior vena cava
S.V.C. = Superior vena cava
R.A. = Right auricle
R.V. = Right ventricle
P.A. = Pulmonary artery



A



B

FIG. 8. Dye dilution curves recorded by ear oximeter showing an early appearance time and a double dip (A and B) indicative of a right-to-left shunt.

extremely difficult to be sure that an auricular septal defect or patent foramen ovale did not permit entry of the catheter into the left auricle before continuing out into the lung field. Thus at times the cardiac catheterization may not give final or decisive findings.

The right auricular pressure is only slightly raised but there is always right ventricular hypertension with pressures ranging from two to nine times the normal systolic value. The pulmonary artery pressure may be slightly lower than that of the right ventricle. Only one autopsied case of pulmonic stenosis in this condition has been recorded[19] and this was a complex malformation. As in the present paper we are concerned only with uncomplicated total drainage anomaly, any fall in the pulmonary artery pressure is not likely to be the result of pulmonary valvular changes. The tricuspid insufficiency present in some patients may explain the phenomenon. Alternately, the tremendous outflow from the right ventricle may produce a relative stenosis at the pulmonary ring.

It has become increasingly apparent that the clinical picture of pulmonary veins into the innominate vein (or left superior vena cava) in children and adults is a clear cut pattern on the basis of x-ray findings alone. The electrocardiogram further assists in the diagnosis and the cardiac catheterization results can thus be predicted. It is therefore questionable now whether

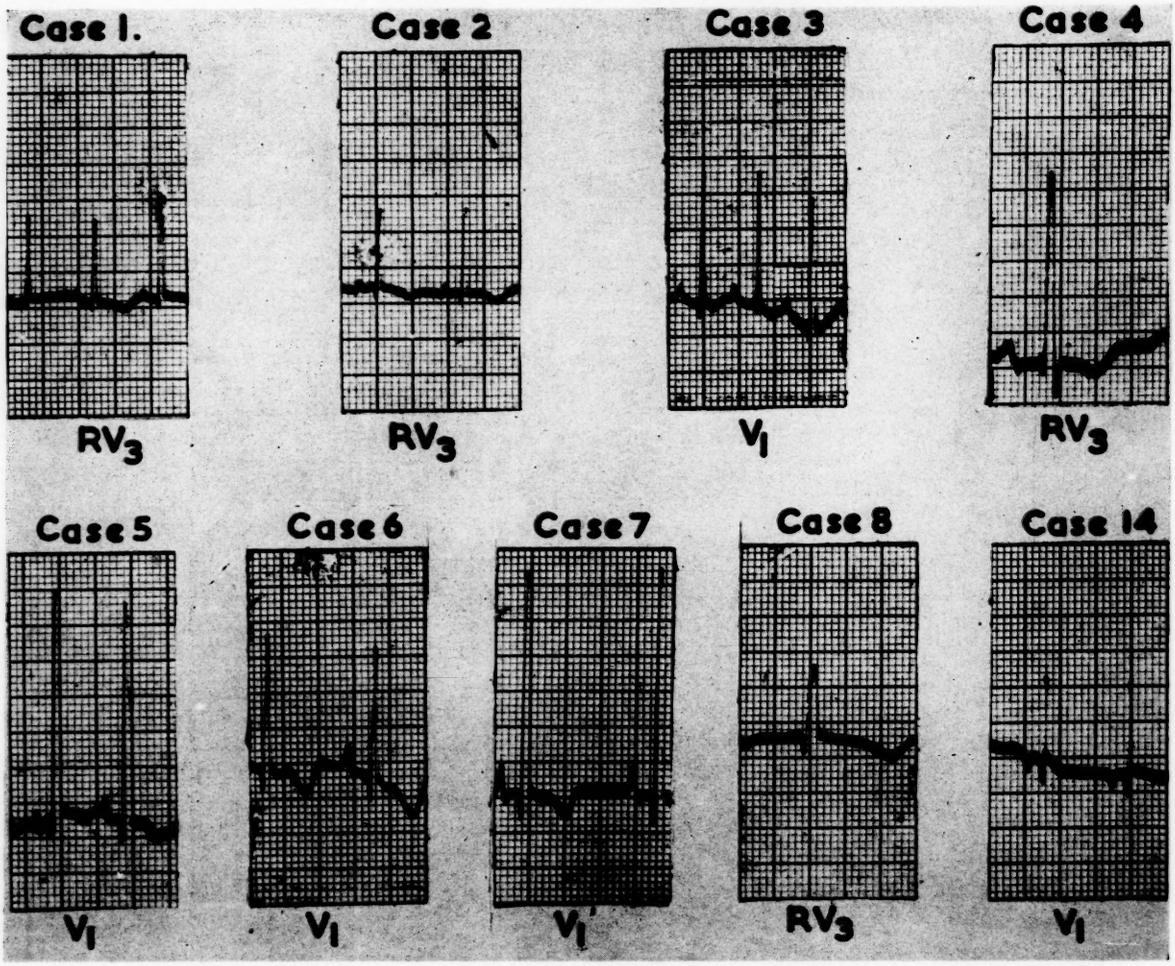


FIG. 9. Segments from electrocardiograms of nine of our patients showing the qR pattern in the right precordial leads.

this investigation is necessary in such cases. However, in infancy the characteristic supracardiac venous collar may be absent and in this age group, as in the remaining varieties of the anomaly, the intracardiac catheter is an indispensable aid to diagnosis.

Since a patent foramen ovale is always present in these infants and children, one would consequently expect it should not be difficult to pass a catheter into the left auricle. We have been able to do this in only one of the four cases we have catheterized. Patent ductus arteriosus has been described in the literature but in our experience this channel has been very small in infants and closed in the older ones. In none of the fully reported cases has there been any direct evidence at catheterization of a patent ductus arteriosus and it would be impossible to rely on blood oxygen analysis to prove the point.

Analysis of blood removed from a systemic artery in thirteen cases available for such study showed an average arterial oxygen saturation of 86 per cent with a range of 63 to 95 per cent. (Fig. 3.) Therefore, in spite of the fact that there is mixing of both circulations in the right auricle, the blood reaching the aorta has a higher oxygen content than one would expect. The mean figure is somewhat lowered by the inclusion of one child, Case 7, who is of considerable interest because no adequate explanation has been found even after autopsy for her marked cyanosis. Bing has shown in two cases that the systemic blood flow is approximately 20 to 75 per cent that of the pulmonary flow.

Oximetry. The ear oximeter* was used in seven patients to follow arterial oxygen saturation at rest and with exercise. In general the resting values approximated those obtained by the Van Slyke analysis of arterial blood. Exer-

* Manufactured by Waters Conley, Rochester, Minn.

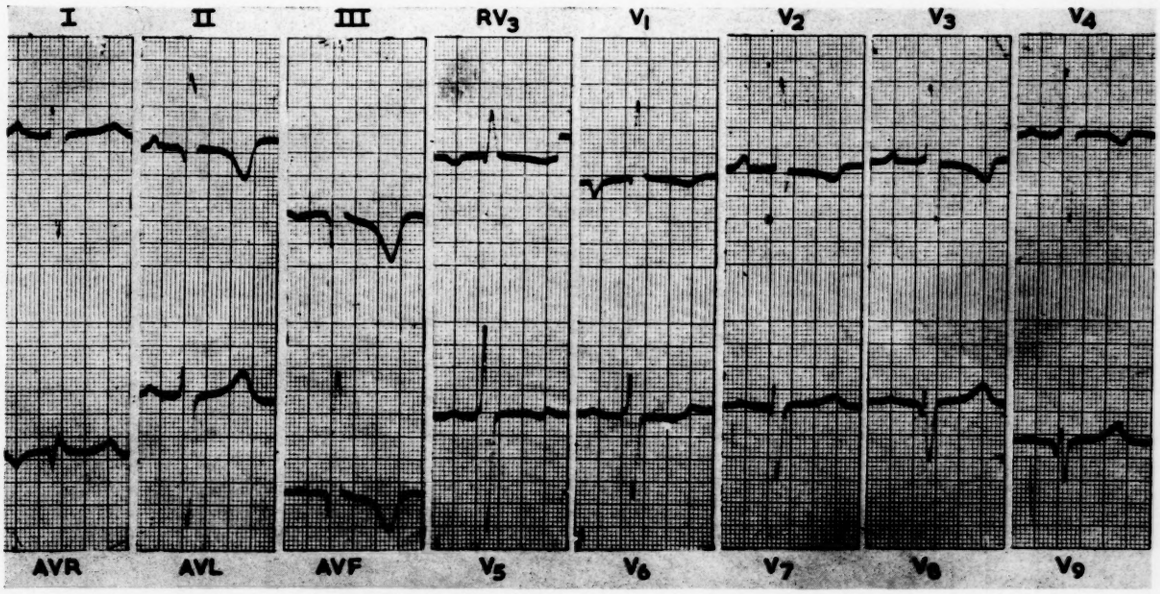


FIG. 10. Case 7, B. P., age seven years. Electrocardiogram with simultaneous leads, February 11, 1952. (For comment, see text.)

cise or crying resulted in slight or no change in three cases. In two there was a fall of 7 to 15 per cent and in another two a rise of 7 to 10 per cent in arterial oxygen saturation. The latter change occurred only in infants under one year of age. The explanation of these variations remains uncertain. Evans blue dye studies were performed in five patients, utilizing the principles outlined by Knutson et al.[21] and Nicholson et al.[22] A modification of the electronic oximeter* designed by Paul[23] was used, an Esterline-Angus recorder reproducing the curve at the ear following intravenous injection of 0.5 mg./kg. of T 1824 (0.5 per cent solution).

In both Cases 7 and 8 (Fig. 8) dye appeared at the ear in shorter time than normally. Both curves show the double dip characteristic of right-to-left shunt and in each case the disappearance time was prolonged in addition. A case of anomalous pulmonary venous drainage cited by Nicholson showed a similar pattern. The first dip (A) is likely to be due to the right-to-left shunt of dye through a patent foramen ovale. The second deflection (B) is probably the result of a further major amount of dye passing through the auricular defect after circulating through the lungs. The delayed disappearance time is a consequence of pooling, recirculation and dilution of the dye within the central circuit.

* Manufactured by Canadian Marconi Co., Montreal, Quebec.

In three other cases dye injection produced the flattened curve of chronic heart failure and the shunt patterns were obscured for this reason.

The Electrocardiogram. The tracings follow a relatively uniform pattern. The axis of QRS shows slight to moderate deviation to the right; in only three cases exceeding +130°. The electrical position of the heart is horizontal in almost all cases. The P waves are abnormally tall and peaked either in the precordial or standard leads or both. In only two instances (Cases 2 and 3) is the height of the P wave within normal limits.

The ventricular complex shows evidence of right ventricular hypertrophy and/or dilatation of marked degree: a high R wave in V_1 and little or no S wave in the same lead; a low R and deep S in V_5 and V_6. AVR shows an R wave of over 5 mm. in two-thirds of our cases. In V_1 the R wave measures 11.0 to 40.0 mm., averaging 21 mm. The S wave is absent in five cases while in the other five its mean value is 3 mm. The R/S ratio in V_1 is thus often infinity. In V_6 the R wave measures 2.0 to 18.0 mm., averaging 8.8 mm. The S wave varies from 5.0 to 40.0 mm. with a mean value of 16.0 mm. The R/S ratio ranges between 0.27 to 2.8 with an average of 0.67.

The striking feature of the electrocardiogram is the presence of a q wave in the right precordial leads. A segment from the precordial leads of our patients is shown in Figure 9.

TABLE III

SUMMARY OF ELECTROCARDIOGRAPHIC FINDINGS

Case	Age	Â QRS	Electrical Position	P_2 (mm.)	R in AVR (mm.)	V_1 R (mm.)	V_1 S (mm.)	V_5 R (mm.)	V_5 S (mm.)	V_6 R (mm.)	V_6 S (mm.)	Q in Rt. Precordial Leads	V.A.T. in V_1 (sec.)	R/S or R/Q in AVR	R/S in V_1	R/S in V_5	R/S in V_6	T Wave: Standard Leads	T Wave: Precordial Leads
1. S. V.	9 days	+130°	H	1.5	7.0	16.0	2.0	14.0	10.0	4.0	7.0	0	0.035	2.3	8.0	1.4	0.57	I flat II − III −	RV_3 to V_6 +
	14 days	+130°	H	2.0	6.0	13.0	3.0	6.0	11.0	3.0	6.0	RV_3	0.035	1.2	4.2	0.55	0.50	I + II + III +	RV_3 to V_2 − V_4 to V_6 +
	2½ mo.	+160°	H	3.5	15.0	40.0	2.0	20.0	19.0	4.0	14.0	RV_3	0.040	3.0	20.0	1.05	0.28	I + II − III −	RV_3 to V_5 − V_6 +
2. B. H.	18 days	+130°	H	1.5	5.5	11.0	0	8.0	19.0	3.0	11.0	RV_3	0.035	2.7	∞	0.42	0.27	I + II + III flat	RV_3 to V_4 − V_5 flat V_6 +
3. M. W.	4 wk.	+130°	H	1.5	4.0	15.0	0	5.0	3.0	4.0	5.0	0	0.040	2.0	∞	1.6	0.80	I flat II + III +	V_1 to V_6 +
	8 wk.	+130°	H	2.0	4.5	19.0	0	10.0	8.0	5.0	8.0	V_1	0.040	1.1	∞	1.25	0.62	I flat II − + III −	V_1 to V_5 + V_6 − +
	9 wk.	+120°	H	2.0	4.0	17.0	0	22.0	6.0	9.0	8.0	V_1 V_2	0.040	0.8	∞	3.6	1.12	I + II + III +	V_1 to V_6 +
4. S. W.	9 mo.	−150°	Int.	2.0	5.5	30.0	8.0	5.0	9.0	2.0	7.0	RV_3 V_1	0.040*	5.5	3.74	0.55	0.28	I + II + III − +	RV_3, V_1 − V_2 − + V_4 to V_6 +
5. L. C.	10½ mo.	±180°	SH	3.0	12.0	29.0	0	18.0	24.0	4.0	12.0	V_1 V_2 V_3 V_4	0.040	6.0	∞	0.75	0.33	I − II − III −	V_1 to V_4 − V_5 − + V_6 +
6. P. R.	2½ yr.	+120°	H	1.0	8.0	18.0	1	21.0	6.0	17.0	6.0	V_1 (rsR′ in V_2)	0.040	1.0	18.0	3.5	2.8	I + II + III − +	V_1, V_2: − V_3 to V_6: − +
7. B. P.	5 yr.	+110°	H	3.0	3.0	26.0	0	19.0	18.0	15.0	21.0	0 (rsR′ in V_1, V_2)	.0 050	1.0	∞	1.05	0.70	I + II − III −	V_1 to V_4 − V_5, V_6 − +
	7 yr.	+110°	H	3.5	3.0	34.0	0	38.0	50.0	16.0	37.0	RV_3 V_1	0.060*	0.6	∞	0.76	0.43	I + II − III −	RV_3 to V_4 − V_5, V_6 − +
8. R. H.	9 yr.	+110°	H	2.5	4.0	18.0	0	18.0	25.0	9.0	21.0	0 (rsR′ in V_1)	0.035*	0.6	∞	0.72	0.43	I + II + III +	V_1 − V_2 − + V_3 to V_6 +
14. M. I.	5 mo. 7 days	+125°	H	1.5	7.0	12.0	0	26.0	54.0	18.0	40.0	RV_3 V_1	0.040	1.4	∞	0.48	0.45	I + II − + III −	RV_3, V_1 − V_2, V_4 + V_5, V_6 − V_3 +
	5 mo. 10 days	+130°	H	1.5	11.0	11.0	0.5	20.0	36.0	18.0	36.0	RV_3 V_1	0.040	1.4	22.0	0.55	0.50	I + II − + III −	RV_3 − V_1 flat V_2 to V_6 +

V.A.T. = Ventricular activation time
* Measured in simultaneous records of precordial leads.

Although small in half the cases, it was quite definite in all but one. It has been suggested that the qR pattern may be preceded by an iso-electric R wave. The simultaneous leads of the electrocardiogram shown in Figure 10 reveal that the q wave in V_1 is inscribed 0.02 sec. after the beginning of the rapid phase of the ventricular complex in V_6. Case 8, in whom no q wave was present in RV_3, V_1 or V_4, showed an rsR′ pattern. A small initial r wave in chest leads, other than RV_3, V_1 and V_2 when a q wave is present, is seen in two additional cases. The T wave is markedly inverted in leads II, III and AVF in half the cases. In the precordial leads the T wave is inverted in RV_3 and V_1 in all except one case. Further, inversion continued as far across the chest as V_4 in four and V_6 in three cases. (Table III.)

TABLE IV

INCIDENCE OF QR PATTERN IN RIGHT PRECORDIAL LEADS IN 145 CASES OF CONGENITAL HEART DISEASE

	Method of Diagnosis	No. of Cases	Age of Patients with q Waves	Age of Group	No. with qR Pattern	Per cent
1. All pulmonary veins into right auricle or tributaries	Postmortem	9	2 wk.–9 yr.	2 wk.–9 yr.	8	89
2. Hypoplasia of the aorta with infantile coarctation	Postmortem	9	3 days–1 mo.	3 days–1 mo.	7	77
3. Pulmonary stenosis with patent foramen ovale	Catheter, operation, postmortem	17	9 mo.–10 yr.	2 wk.–11 yr.	8	47
4. Auricular septal defect	Catheter	14	3–10 yr.	12 days–17 yr.	4	28
5. Eisenmenger's complex	Catheter, postmortem	16	3 mo.–12 yr.	2 mo.–13 yr.	4	25
6. Pure pulmonary stenosis	Catheter, clinical	13	2½–14 yr.	9 mo.–14 yr.	3	24
7. Tetralogy of Fallot	Operation	34	6 mo.–3 yr.	2 wk.–15 yr.	6	18
8. Transposition of great vessels	Postmortem	16	.....	2 days–13 mo.	0	0
9. Tricuspid atresia	Postmortem	14	.....	1 day–13 yr.	0	0
10. Miscellaneous:						
a) Non-functioning left ventricle, Dextroposition of aorta Pulmonary stenosis	Postmortem	1	9 mo.	.....	1	..
b) Congenital tricuspid incompetence	Postmortem	1	13 mo.	.....	1	..
c) Pulmonary and tricuspid stenosis	Postmortem	1	8 mo.	.....	1	..

COMMENT

The diagnosis of total pulmonary venous drainage into the right auricle or its tributaries offers scope for many of the modern procedures available for the diagnosis of congenital heart disease.

First of all one must take into account the clinical picture which, while not clear cut, will frequently give a lead in making a correct diagnosis. The defect may be found in all ages from birth to twenty-seven years but it is commonly fatal in the first six months of life. One therefore looks for an infant who is not significantly cyanosed. If failure is present, cyanosis will be noted in most instances. Usually there will be an inadequate weight gain. There may be either no heart murmur or a very modest systolic blow audible between the second and fourth left interspaces. Occasionally a continuous murmur of distinct diagnostic significance may be recorded in the pulmonary area. Under the fluoroscope the heart will usually show enlargement, the pulmonary artery will bulge considerably and the hilar shadows will be large and usually pulsate briskly.

The electrocardiogram proves very useful in leading one to suspect the diagnosis of total anomalous pulmonary venous drainage. It will reveal increasingly marked right ventricular hypertrophy and a qR pattern in the right precordial leads. The presence of the latter inscription seemed to have more diagnostic significance than other aspects of the electro-

cardiogram. This pattern usually appeared in the early weeks of life and persisted. To establish the frequency of the qR pattern in the right precordial leads in congenital heart disease we reviewed the electrocardiograms in 145 cases. (Table IV.) In all groups the diagnosis was confirmed by postmortem, cardiac catheterization or operation. It can be seen that cases with anomalous pulmonary venous drainage had the highest percentage. Those with aortic hypoplasia were next in frequency while cases of pulmonary stenosis with patent foramen ovale occupied third place. No q wave was seen in the right precordial leads of cases with uncomplicated complete transposition of great vessels or tricuspid atresia. Another diagnostic point was that the qR pattern appeared earlier in cases of anomalous pulmonary venous drainage than in the group with pulmonary stenosis but no earlier than those with aortic hypoplasia. Thus in the first few weeks of life the qR pattern is likely to be due to aortic hypoplasia or aberrant pulmonary venous return.

Pathologically, there is evidence associating the qR pattern with a dilated right auricle in the presence of right ventricular hypertrophy.[24] The right heart chambers in cases of complete anomalous pulmonary venous drainage are tremendously dilated and the encountered high incidence of qR inscription in these patients over the right precordium lends support to this finding. The same is true in cases of hypoplasia of the aorta and, possibly to a lesser degree, in pulmonary stenosis with patent foramen ovale.

The electrogenesis of the pattern in right precordial leads has been discussed by several authors. Goldberger[25] ascribes the changes to marked cardiac rotation. Even if it were true that the left ventricular epicardial potential had a qR pattern it is quite certain in the cases under discussion that, as the left ventricle is greatly underdeveloped, no amount of rotation of the heart could explain its inscription over the right chest. Myers[26] and Fowler et al.[27] believe that the electrocardiographic changes may be due to a reversal of activation of the ventricular septum. Intracavity leads from both ventricles should help clarify this point. Sodi-Pallares[24] on experimental evidence states that the dilated right auricle allows transmission of the q wave from the right upper portion of the ventricular septum.

Catheterization of the heart will show a rise in oxygen content on entering the right auricle or in one of its tributaries. When the origin of the rise is clear, the diagnosis will be evident but occasionally difficulties will occur. Possibly a third of the cases will present no problem since the x-ray picture will be pathognomonic of pulmonary venous drainage into the left innominate vein. The other sites of drainage can usually be identified by catheterization. In early infancy the major problem lies in differentiating cases of aortic hypoplasia or atresia or infantile type of coarctation. These babies are seen in heart failure often with minimal cyanosis, marked cardiac enlargement and heavy lung vascularity. Their electrocardiograms show marked right ventricular hypertrophy with a qR pattern in the right precordial leads. However, the heart enlargement is exceedingly rapid and the life duration is much shorter. The qR pattern is an earlier feature and inverted T waves in the left precordial leads are frequent (seven of nine cases).

The chief problem in differential diagnosis in older infants and children lies between anomalous pulmonary venous drainage into the right auricle or coronary sinus and auricular septal defect. Certain clinical data will aid in this differentiation. In the auricular septal defect the hilar shadows are usually smaller and show less significant pulsations. The patient is usually more active and less dyspneic than in the pulmonary vein anomaly. There is usually not a drop in oxygen content of the arterial blood with exercise in the auricular septal defects while such may occur in the case of the venous anomaly. The arterial oxygen saturation is usually normal in auricular septal defect and is commonly lower than normal at rest in the venous anomaly. The electrocardiogram may be distinctly helpful especially when a RsR′ pattern is present, which is a much more common finding in auricular septal defect than in the pulmonary venous anomaly. The presence of a qR pattern in the right precordial leads will suggest anomalous pulmonary venous drainage rather than an auricular septal defect, although this pattern may occasionally occur in the latter condition. During catheterization in patients with auricular septal defect we have on occasion found a raised oxygen content in the inferior vena cava near the entrance to the right auricle. This should be taken into account in assessing the possibility of pulmonary venous drainage into the ductus venosus or portal vein.

A clear understanding of anomalous pulmo-

nary venous drainage is of more than academic interest since some authors have suggested and used surgical technics for these cases.[17,18] Muller records anastomosing the tip of the left auricular appendage to the side of the anomalous pulmonary venous trunk with some clinical improvement of the patient. Three patients have been operated on in our group and all died. Two died before operation could be completed and the third died one to two hours postoperatively. In the first two an end-to-side anastomosis between the anomalous vein and the left auricular appendage was carried out but the partial constriction of the anomalous vessel in order to produce the anastomosis was sufficient to slow the heart and eventually cause cardiac arrest. In the third case, after the operation had been completed it was decided to ligate the anomalous pulmonary vein beyond the point of the anastomosis in order to route all the blood from the anomalous vessel directly into the left auricle through the left auricular appendage. The patient died an hour or two postoperatively. At postmortem we reached the conclusion that death was probably due to inadequate blood flow through the new channel. If one refers to Table 1 it will be seen that the waist of the left auricular appendage is usually narrower than the anomalous pulmonary vein so that the left auricular appendage cannot carry as much blood as the anomalous channel. Another problem arises from the fact that it is difficult to produce a sufficiently large anastomosis with the left auricular appendage. Furthermore the left auricle is underdeveloped and thus cannot be expected to carry the total blood flow adequately. For these reasons we believe that the patients who are in fair health and reasonably active should probably not be operated upon at this state of our knowledge. In the patients who are doing poorly a large end-to-side anastomosis with the left auricular appendage would appear to be the operation of choice. When the anastomosis is completed, the patient will be left with the anomalous vein intact but will have an added opening into the left auricle. For the reasons mentioned we believe the anomalous vein should not be ligated immediately even if an adequate opening has been produced into the left auricle.

SUMMARY

The literature concerning total uncomplicated anomalous pulmonary venous drainage is reviewed. Fourteen cases in children, thirteen proven by autopsy, are added to this group.

The main clinical findings in infants and children are lack of clinical cyanosis and failure to thrive. Murmurs may be absent or faint initially. Later a parasternal systolic murmur between the second and fourth left interspaces becomes increasingly evident. Diastolic murmurs are occasionally heard. A venous hum was audible in the pulmonary area in about one-fourth of the authors' cases and is specific to one particular type.

The radiologic picture varies with the anatomical type. When the pulmonary veins drain into a left superior vena cava, a characteristic mediastinal venous shadow is present except in the first few months of life. Increasing cardiac enlargement after birth is the rule. Lung vascularity is markedly increased.

The electrocardiogram shows marked right ventricular hypertrophy with a qR pattern and inverted T waves in the right precordial leads.

Cardiac catheterization is of value but has a number of limitations.

The chief diagnostic difficulty lies in separating this anomaly from aortic hypoplasia in infancy and auricular septal defect in older children.

Surgical correction of the condition would seem theoretically possible because of the close proximity of the left auricular appendage to the anomalous venous trunk. However, the small waist of the left auricular appendage, the difficulty in making a large enough anastomosis, the small left auricle and ventricle all militate against successful surgery.

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Determination of Total Lung Capacity in Disease from Routine Chest Roentgenograms*

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METHODS commonly employed for determination of total lung capacity are either tedious or expensive. A number of investigators have studied the relations of the lung capacity and its subdivisions to volumes calculated from measured areas on specially taken chest roentgenograms (and external body measurements) of healthy subjects, but few have described these relationships in disease and none to our knowledge have studied the usefulness of chest x-rays taken with routine technics, without special preparation of or instruction to the subject, as aids in investigation of disordered pulmonary physiology. In this paper studies are presented on the feasibility and accuracy of total lung capacity determination in disease by volumetric measurement of routine postero-anterior and lateral chest roentgenograms.

Our terminology for the volumetric subdivisions of the gaseous contents of the lungs is that proposed by Pappenheimer[23] as a system of standard nomenclature. Comroe's manual[7] is a comprehensive source of the technical aspects of pulmonary function studies. The value, clinical and otherwise, of determinations of the total lung capacity and its subdivisions is generally accepted and is reviewed in recent publications.[2,3,8,10,20,26,31]

Discussions of statistical theory and practice§ related to determination of correlation between two supposedly related sets of data, and the significance thereof, may be found in the monographs of Croxton and Cowden,[11] Peatman,[24] Hill[15] and Winsor.[30] Gilson and Hugh-Jones[13] present a useful discussion of the values and hazards of the use of regression equations for the prediction of "normal" values to be expected in an individual, pointing out that the error of the predicted value increases *very* rapidly as r, the coefficient of correlation, decreases; for example, the error in prediction of vital capacity with the highest correlations previously reported is such that unless the observed figure differs from the predicted by more than 20 per cent, abnormality cannot be regarded as likely. Hill[15] emphasizes the danger of straining the interpretation of statistical data such as the correlation coefficient.

Among informative papers regarding normal value ranges for the total lung capacity and its subdivisions are those of Baldwin, Cournand and Richards,[2] Birath,[5] Christie,[6] Gilson and Hugh-Jones,[13] Herrald and McMichael,[14] Hurtado and co-workers,[16–19] Kaltreider, Fray and Hyde,[20] Robinson[25] and Whitfield, Waterhouse and Arnott.[29] Values for healthy adults of both sexes and in older and younger age groups have been established. Steward[27] and certain others have studied children but juvenile norms are not as definite.

HISTORY

Development of methods for determination of residual volume[1,6,7,12] and thereby of total lung capacity was paralleled by efforts to predict expected values for the lung capacity and its subdivisions from various combinations of physical characteristics of the individual subject, e.g., age, height, weight, bodily surface area and others. Lundsgaard and Van Slyke[21] were among the first to suggest anything of this

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nature for total capacity, proposing in 1918 that lung volumes more or less closely followed the external chest size measured in three diameters. In 1939 Aslett, Hart and McMichael[1] reviewed previous attempts to correlate vital capacity and various physical measurements.

TABLE 1

COEFFICIENTS OF CORRELATION OBSERVED BY PREVIOUS INVESTIGATORS BETWEEN TOTAL LUNG CAPACITY, VITAL CAPACITY AND VARIOUS PHYSICAL AND RADIOLOGICAL MEASUREMENTS

Physical and Radiological Characteristics	Aslett et al. 64 Males	Hurtado et al. 50 Males	Kaltreider et al. 50 Males	Hurtado et al. 50 Females
Correlations with Total Capacity				
Standing height	+0.66	+0.48	+0.62	+0.66
Stem height	+0.66	.....	.....	.....
Weight	+0.55	+0.01	+0.36	+0.18
Surface area	+0.64	+0.15	+0.44	+0.36
Chest circumference	+0.53	+0.14	.....	.....
Area lung fields	+0.65	+0.55	+0.79	+0.63
Radiological chest volume	+0.80	+0.61	+0.85	+0.63
Correlations with Vital Capacity				
	66 Males			
Standing height	+0.70	+0.55	+0.64	+0.51
Stem height	+0.78	.....	.....	.....
Weight	+0.57	+0.14	+0.31	+0.26
Surface area	+0.67	+0.28	+0.45	+0.34
Chest circumference	+0.51	+0.16	.....	.....
Area lung fields	+0.59	+0.68	+0.68	+0.60
Radiological chest volume	+0.63	+0.72	+0.73	+0.71

Source: ASLETT, E. A., HART, P. D'A. and MCMICHAEL, J. The lung volume and its subdivisions in normal males. *Proc. Roy. Soc., London, s.B.*, 126: 502, 1939. (Headings modified.)

Binger and Brow[4] suggested in 1924 that the lung capacity might be inferred from the area of the lung fields on chest roentgenograms. (Fig. 2A.) One of the first definitive works statistically correlating a large number of physical and radiological measurements with the lung capacity and its subdivisions was that of Hurtado and Fray.[17] Their paper, published in 1933, had been immediately preceded by extensive investigation of the normal ranges for the pulmonary volumes by Hurtado and Boller,[16] and was shortly followed by papers studying the same data as obtained in different age groups and the two sexes.[19,20] Correlations between the total lung capacity and its subdivisions and radiological and physical measurements were further examined by several British workers, namely Aslett, Hart and McMichael in 1939,[1] Gilson and Hugh-Jones in 1949,[13] and Wade and Gilson in 1951.[28]

RADIOLOGICAL CHEST VOLUME (RCV)

The measurement of "radiological chest volume" was introduced by Hurtado and Fray[17] in their attempts to find an accurate method of predicting the size of the pulmonary volumina to be expected in an individual, were he in health. Subsequent workers have used essentially the same technic in determining RCV in healthy subjects, the important points of which are: (1) planimetric measurement of "lung field area" on specially taken chest films, often anteroposterior in the recumbent position with coaching by the examiner to insure the presence of maximal inspiration; (2) inclusion of the cardiomediastinal area with that of the remainder of the thoracic cavity; and (3) the use of calipers (commonly an obstetric pelvimeter) to measure the anteroposterior diameter of the chest externally at an inconstant level (the nipple line), again coaching the respiratory phase of the subject. The area measurement multiplied by the linear produces the RCV, a volumetric figure. The course followed by the point of the planimeter in determining "area of lung fields" by the technic of Hurtado and Fray is shown in Figure 2B.

PREVIOUS CORRELATIONS

Table 1, from the review of Aslett and coworkers,[1] summarizes the coefficients of correlation obtained in his laboratory and by his predecessors in investigations in which total lung capacity and vital capacity were compared against a number of physical and radiological measurements in healthy subjects. Statistical tests of significance are not included in this table but are present in varying quantity in the original papers and demonstrate the higher coefficients to be reliable.

In Table 1 the highest coefficients of correlation (r) between vital capacity and physical or radiological measurements are noted to occur with stem height (+0.78) and RCV (+0.73). A greater correlation was observed between total lung capacity and RCV in males (+0.80 and +0.85). The most consistent relation obtained by Hurtado and Fray was between vital capacity and RCV ($r = +0.7174 \pm 0.0467$*). Accordingly they recommended that normal vital capacity for the individual be predicted from the

* Probable error.

appropriate regression equation, and total lung capacity then be derived from the normal percentage of total capacity believed to be occupied by vital capacity in the age and sex group under consideration. Kaltreider, Fray and Hyde[20] obtained an r of $+0.8497 \pm 0.0265$* for the relation between RCV and total lung capacity in older males (ages 38 to 63). They suggested that the total capacity be calculated from the RCV directly by use of the regression equation, which in their series was:

$$\text{Total lung capacity, liters} = \frac{\text{RCV, liters}}{0.31} + 0.71$$

Their coefficients for females and younger males were of the same order of magnitude but slightly smaller. The total lung capacity was determined by the Christie method[6] by Hurtado and Kaltreider; the constant-volume modification thereof[14] was employed by Aslett and co-workers.

Gilson and Hugh-Jones[13] presented data on the reproducibility of radiological chest volume determinations. By using "pole-within-circle" planimetry, the measurement of lung field area (including the cardiomediastinal volume) could be repeated to within ½ per cent; on the other hand, caliper measurement of the antero-posterior diameter of the chest could not be made with any greater accuracy than 0.5 cm. in 25 cm., the latter being an average measurement. The most important source of variation between repeated estimations of the RCV in an individual was found to be variation between roentgenograms—"presumably due to the subject not always being in full inspiration." From an analysis of variance of forty-eight readings of RCV in sixteen subjects into "between patients" and "between x-rays," they found that taking the mean of three x-rays gave a standard error of 58 cc. in chest volume estimation or, alternatively, an error of 71 cc. if the mean of two radiological volumes was taken. As many workers have demonstrated that the standard error in determination of either vital capacity or functional residual capacity is about 100 cc., whether a constant-volume closed circuit or an open circuit method is used for the non-spirometric determination,[5,6,9,13,22] it will be seen that in health a radiological measurement may be comparable in error to a gaseous measurement of total lung capacity. The factor of excessive roentgen exposure prevents testing of chest film reproducibility by taking large numbers of pictures of a single individual.

Wade and Gilson,[28] however, in a paper published in 1951 recommended spirometric checking and timing of film exposure as an aid in obtaining accurate RCV values.

Aslett, Hart and McMichael[1] found their best correlations for prediction of values for the total lung capacity and its subdivisions in health between total capacity and RCV,* and between vital capacity and stem height. Their regression equations were as follows:

$$\text{Total lung capacity, liters} = \frac{\text{(RCV, cubic inches)}}{0.00615} + 0.48$$

$$\text{Vital capacity, liters} = \frac{\text{(stem height, inches)}}{0.324} - 7.52$$

As an illustration of correlations and regression equations relating vital capacity and certain non-radiological measurements, the work of Baldwin, Cournand and Richards[2] may be cited. They performed vital capacity determinations in fifty-two males and forty-two females in health, and placed their subjects in three groups according to age. Their coefficients of correlation for supine vital capacity per centimeter of height with age, which were individually significant, were -0.428 for males and -0.505 for females. Separate regression equations were derived for the genders. Baldwin and co-workers then predicted the total lung capacity for the subject using the data of Kaltreider, Fray and Hyde[20] which determined, from a study of 150 normal adult males and females, that the ratio

$$\frac{\text{residual volume}}{\text{total capacity}} \times 100$$

varied in rather constant fashion with age.

AVENUES OF APPROACH

In considering the previous correlations observed between the total lung capacity and the radiological chest volume, the authors wondered if *special* chest films were necessary to obtain good correlation. Further, we were of the opinion that greater correlation might be obtained by changing the method of measuring the antero-posterior diameter of the chest, which was esti-

* Probable error.

* The chest roentgenograms used in Aslett's study were taken at a distance of 4½ feet, which produces a thoracic area some 4 per cent larger than that obtained when a 6 foot distance is used.

mated at the inconstant level of the nipple line with coarsely graduated calipers (pelvimeters) by previous investigators, and shown to be a poorly reproducible technic by Gilson and Hugh-Jones.[13] We had noticed in diseases such as pulmonary fibrosis with infection, bronchiectasis or empyema, when there was more or less replacement or compression of aerating lung parenchyma, that use of conventional formulas for prediction of the expected pulmonary volumina (as those based on height and age) often left doubt as to how much of a given percentage decrease in total lung capacity was due to replacement of ventilated parenchyma by other material frequently neither circumscribed nor quantitatively estimable by sight from the chest roentgenogram. In other words, it was believed that if a total lung capacity figure derived from radiological measurement of the individual thorax were combined with an expected value derived from group regression equations such as those based on height and age of subject, the disposition of "lost gas volume"[7] might be decided more accurately.

The authors were unable to find a previous study in the literature in which two series of radiological chest volume determinations in the same group of diseased subjects were compared for degree of correlation with total lung capacity, with one series of RCV measurements including the cardiomediastinal volume in the RCV (as in the method of Hurtado and Fray[17]) and the other subtracting this entity. Further, given a patient with a circumscribed and therefore outlinable area of disease on the postero-anterior chest roentgenogram, such as lobar atelectasis, pneumothorax or a lung abscess, would it add accuracy in RCV determination to subtract the radiological volume of the diseased tissue? Uncircumscribed pathologic processes such as diffuse tuberculosis of course would not be amenable to planimetric tracing. Lastly, in patients who either had no pulmonary disease or such a process as diffuse emphysema in which ventilating parenchyma was not replaced, could sufficient correlation be obtained between the total capacity determined by gas washout (or dilution) methods and capacity determined from the RCV to enable $\frac{\text{residual volume}}{\text{total capacity}}$ ratios to be determined with reasonable reliability from performance of the vital capacity on a simple spirometer and determination of total capacity from routine chest x-rays? Such a procedure might offer a rapid method for screening large numbers of individuals for an increase in the ratio.

METHODS

With these questions in mind we studied seventy-seven consecutive patients who met the two criteria of (1) having had total lung capacity determinations in this laboratory and (2) having routine postero-anterior and lateral chest roentgenograms on file in the Department of Radiology of Albany Hospital. The chest films of one individual were in partial expiration on gross inspection and were discarded; this was the only selection made, leaving seventy-six essentially unselected cases as subject matter for the study.

The vital capacity and its subdivisions were determined in these patients by conventional spirometry with the patient supine, correcting the observed gas volumes of BTPS.* Functional residual capacity was determined in the supine position by the method of Darling et al.[9,12] and, all determinations being made in duplicate, the same degree of reproducibility was observed in this laboratory as by the originators of the method.

In Table II observed total lung capacity and observed vital capacity are listed for each subject. The latter is included should the residual volume percentages be desired for certain cases by the reader. In the adjacent two columns are listed "predicted total capacity" and "predicted vital capacity" for each subject. These values were arrived at as follows: for vital capacity, the regression equations of Baldwin, Cournand and Richards[2] were used; the values for predicted total capacity were then derived from the predicted vital capacities by employing the ratios for $\frac{\text{residual volume}}{\text{total capacity}}$ determined in a large series of healthy subjects by Kaltreider, Fray and Hyde.[20] These predicted values are included to provide an estimate of bodily size and habitus in those subjects for whom this information may be desired.

The chest films employed were all taken before this study was contemplated, insuring that no patient had received other than the routine instructions and positioning given by the x-ray technician. Two films (erect position) were used

* Body temperature, ambient pressure, saturated with water vapor.

TABLE II

RADIOLOGICAL CHEST VOLUME (RCV) AND ITS MODIFICATIONS, WITH DETERMINED AND PREDICTED TOTAL LUNG CAPACITY AND VITAL CAPACITY, IN SEVENTY-SIX PATIENTS WITH VARIOUS TYPES OF PULMONARY DISEASE

No.	Patient (Females in Parentheses)	Age	Diagnosis	Determined Values		Predicted Values		Antero-posterior Diameter of Chest (cm.)	RCV_1* (L.)	RCV_2 (RCV_1 Minus Radiological Volume of Disease) (L.)	RCV_3 (RCV_1 Minus Radiological Volume of Heart and Mediastinum) (L.)
				Total Capacity (L.)	Vital Capacity (L.)	Total Capacity (L.)	Vital Capacity (L.)				
1	C. B.	48	Emphysema	6.40	2.10	5.03	3.85	22.8	17.26	.....	12.68
2	T. C.	55	Emphysema	6.17	2.30	5.25	3.64	23.0	17.49	.....	13.06
3	A. C.	69	Emphysema	6.95	1.15	4.90	3.39	25.5	17.47	.....	12.50
4	A. C.	56	Emphysema	6.48	2.80	5.96	4.12	22.0	18.37	.....	13.03
5	B. D.	55	Emphysema	6.63	2.90	5.27	3.65	22.5	14.70	.....	11.92
6	G. D.	62	Emphysema	6.61	1.84	4.94	3.42	23.5	15.42	.....	10.72
7	(A. G)		Asthma, bronchitis	4.42	2.80	3.88	2.68	18.0	9.56	.....	6.04
8	V. G.	52	Emphysema	6.03	2.30	5.55	3.84	22.0	14.41	.....	9.70
9	T. J.	55	Emphysema	5.82	3.09	5.58	3.86	26.0	17.79	.....	12.11
10	J. K.	57	Emphysema	7.87	2.25	5.32	3.68	24.0	23.45	.....	17.25
11	E. M.	58	Emphysema	6.15	2.06	5.50	3.80	25.5	20.76	.....	15.00
12	K. M.	64	Emphysema	3.98	1.50	5.06	3.50	20.0	11.11	.....	7.54
13	J. P.	63	Emphysema	5.56	2.15	5.13	3.55	24.5	17.71	.....	12.82
14	J. P.	64	Emphysema	5.15	1.85	5.10	3.53	24.5	16.12	.....	11.30
15	J. P.	64	Emphysema	5.17	2.04	5.10	3.53	24.5	14.13	.....	9.91
16	W. S.	32	Emphysema	7.09	4.92	5.46	4.37	21.5	15.95	.....	11.39
17	T. V.	52	Emphysema	6.34	2.82	5.65	3.91	23.5	16.49	.....	9.58
18	(P. W.)	35	Emphysema	4.13	1.30	3.94	3.02	20.0	12.71	.....	9.43
19	(L. T.)	20	Functional disorder	5.02	3.85	4.17	3.34	18.0	8.88	.....	6.38
20	A. T.	24	Pectus excavatum	4.98	2.78	5.85	4.68	17.0	12.20	.....	8.89
21	D. W.	18	Pectus excavatum	5.56	3.74	5.25	4.20	13.4	10.88	.....	6.95
22	W. A.	29	Bronchiectasis	6.24	4.43	5.57	4.46	20.2	14.62	.....	10.79
23	A. D.	60	Bronchiectasis	4.19	2.40	4.84	3.35	23.5	26.10	25.59	21.33
24	T. F.	26	Bronchiectasis	5.16	2.52	5.34	4.27	22.0	13.72	.....	9.24
25	(M. F.)	32	Bronchiectasis	3.34	2.54	3.60	2.88	22.0	11.75	.....	7.68
26	(V. K.)	37	Bronchiectasis	5.29	3.60	4.07	3.12	17.3	12.59	.....	9.73
27	T. K.	32	Bronchiectasis	4.11	1.95	3.95	3.16	18.0	10.12	.....	6.98
28	(R. M.)	25	Bronchiectasis	2.99	2.22	3.75	3.00	15.0	7.54	.....	5.21
29	(A. N.)	18	Bronchiectasis	4.54	3.40	4.37	3.50	18.0	9.66	.....	6.50
30	L. O.	56	Bronchiectasis	3.94	2.35	5.09	3.52	19.0	9.37	.....	6.30
31	(T. S.)	32	Bronchiectasis	4.29	2.92	3.88	3.10	19.0	10.61	.....	7.44
32	(E. S.)	36	Bronchiectasis	4.49	1.65	3.73	2.86	20.5	12.67	.....	9.88
33	(P. S.)	45	Bronchiectasis	3.65	2.27	3.65	2.76	15.0	8.47	.....	6.03
34	C. D.	48	Bronchogenic carcinoma	5.90	3.18	4.95	3.79	22.0	13.80	.....	8.84
35	J. D.	67	Bronchogenic carcinoma	5.35	3.52	4.94	3.42	20 0	14.26	12.96	9.93
36	M. F.	59	Bronchogenic carcinoma	3.28	2.50	5.45	3.77	22.0	17.55	.....	12.90
37	T. G.	67	Bronchogenic carcinoma	4.86	2.67	5.06	3.50	19.0	12.10	11.18	8.50
38	W. J.	65	Bronchogenic carcinoma	4.03	1.71	5.14	3.56	20.0	12.62	.....	7.96
39	J. K.	44	Bronchogenic carcinoma	6.00	3.90	5.26	4.03	25.0	15.81	.....	11.44
40	C. M.	55	Bronchogenic carcinoma	4.90	2.02	5.36	3.71	23.0	15.30	.....	11.10
41	(D. P.)	46	Bronchogenic carcinoma	2.96	0.95	3.56	2.73	23.0	13.30	9.99	8.51

TABLE II (*Continued*)

No.	Patient (Females in Parentheses)	Age	Diagnosis	Determined Values		Predicted Values		Antero-posterior Diameter of Chest (cm.)	RCV_1* (L.)	RCV_2 (RCV_1 Minus Radiological Volume of Disease) (L.)	RCV_3 (RCV_1 Minus Radiological Volume of Heart and Mediastinum) (L.)
				Total Capacity (L.)	Vital Capacity (L.)	Total Capacity (L.)	Vital Capacity (L.)				
42	L. R.	65	Bronchogenic carcinoma	5.30	2.80	5.32	3.68	25.5	17.12*	.....	9.75
43	A. R.	48	Bronchogenic carcinoma	5.07	2.30	4.87	3.73	23.0	11.89*	.....	7.14
44	P. R.	54	Bronchogenic carcinoma	5.29	2.20	5.63	3.89	23.5	15.65	.....	10.79
45	(P. B.)	23	Pulmonary tuberculosis	4.51	3.10	4.14	3.31	16.0	8.34*	.....	5.83
46	(J. F.)	18	Pulmonary tuberculosis	2.86	1.66	4.08	3.26	15.7	9.23*	.....	6.91
47	(H. H.)	32	Pulmonary tuberculosis	3.73	2.40	3.83	3.06	18.0	9.24*	.....	6.56
48	H. J.	35	Pulmonary tuberculosis	5.29	3.19	5.50	4.21	21.0	13.90	13.27	10.36
49	J. L.	60	Pulmonary tuberculosis	4.68	2.58	4.99	3.45	23.0	14.31*	.....	10.19
50	C. M.	21	Pulmonary tuberculosis	5.22	3.40	5.43	4.34	20.3	12.94	10.70	9.01
51	R. S.	51	Pulmonary tuberculosis	8.22	2.73	5.39	3.73	22.0	18.90*	.....	12.95
52	J. S.	32	Pulmonary tuberculosis	5.18	4.19	5.27	4.21	22.0	13.63*	.....	9.55
53	(J. F.)	18	Lobectomy	2.69	1.91	4.08	3.26	15.7	7.73	.....	5.39
54	A. F.	37	Lobectomy	4.92	2.80	5.32	4.08	18.5	11.58	.....	7.95
55	L. G.	56	Lobectomy	4.97	2.60	5.40	3.74	23.0	16.18	.....	11.62
56	(N. M.)	30	Lobectomy	3.25	2.20	3.58	2.86	15.5	5.55	.....	3.76
57	(E. M.)	48	Pneumonectomy	2.70	1.07	3.56	2.73	20.0	4.02	.....	4.02
58	G. M.	7	Pneumonectomy	1.87	1.15	....	....	13.0	1.86	.....	1.86
59	(G. N.)	56	Pneumonectomy	3.00	1.45	3.79	2.62	19.0	3.21	.....	3.21
60	(A. N.)	19	Lobectomy	4.04	2.90	4.37	3.50	18.0	10.00	.....	6.84
61	(R. S.)	27	Pneumonectomy	1.88	1.26	3.78	3.02	17.5	5.37	.....	5.37
62	H. S.	37	Pneumonectomy	3.67	2.70	5.14	3.94	20.0	5.16	.....	5.16
63	G. S.	51	Pneumonectomy	3.14	1.50	5.40	3.72	19.0	2.84	.....	2.84
64	R. V.	50	Pneumonectomy	2.66	1.57	5.41	3.75	18.0	4.34	.....	4.34
65	C. B.	57	Pneumonitis with cyst	5.19	2.05	5.30	3.67	18.8	11.43	10.47	7.63
66	G. D.	49	Abscess	5.48	3.20	4.57	3.50	22.0	21.43	20.11	17.33
67	(M. G.)	45	Widened mediastinum	2.25	0.82	3.37	2.58	16.6	8.21	.....	4.37
68	(A. H.)	58	Emphysema with blebs	5.54	1.22	3.60	2.44	24.0	15.78	13.88	10.87
69	W. H.	42	Cysts, pneumonitis	3.47	1.17	5.24	4.02	23.0	19.60	18.23	15.35
70	R. J.	19	Spontaneous pneumothorax	5.54	3.96	5.75	4.60	20.5	14.63	14.16	10.73
71	(N. L.)	8	Fibrocystic disease	2.07	0.79	....	....	15.0	4.21*	.....	3.14
72	E. M.	70	Pneumonitis	5.40	3.32	5.14	3.56	20.0	14.78	14.12	10.32
73	T. P.	30	Actinomycosis	5.97	4.49	5.39	4.31	23.0	14.77	11.28	10.60
74	(M. S.)	65	Esophageal carcinoma	3.30	1.94	3.58	2.48	21.0	10.94	.....	6.93
75	R. S.	39	Chest deformity, cor pulmonale	2.10	1.07	4.94	3.78	17.0	8.34	.....	4.55
76	E. V.	63	Abscess	3.87	2.25	4.98	3.44	20.5	11.72	10.55	9.81

* Asterisk indicates diffuse disease.

for each patient: (1) a routine postero-anterior film of the chest and (2) a routine lateral chest film. The latter were right laterals unless the disease was on the left side. The x-ray technics used are believed to be fairly standard over the country for routine chest roentgenograms and are presented in Figure 1.

In measuring the areas of the lung fields, cardiomediastinum and any suitable areas of disease on the postero-anterior chest film a compensating polar planimeter measuring in square centimeters was used.* Area measurements were reproducible within 1.0 sq. cm.

Our technic for measuring the "area of the lung fields" (including cardiomediastinal area) was that of Hurtado and Fray,[17] modified only to the extent that routine postero-anterior instead of special anteroposterior films were used. (Fig. 2B.) To obtain the cardiomediastinal area, the tracing point of the planimeter was placed at the junction of the shadows of the right heart border (or vertebral-mediastinal shadow), and right hemidiaphragm, moved up along the right heart border, up the right side of the mediastinal shadow to the point of intersection with a straight horizontal line passing from one pleural dome to the other (used previously in measuring the "area of the lung fields"), across this line to the left border of the mediastinal shadow, down its left border, along down the lateral border of the shadow of the left side of the heart to the junction of the cardiac right hemidiaphragmatic shadow; then across a straight horizontal line to the left, to the starting point. (Fig. 2C.)

A different technic from that of previous investigators was employed in determining the anteroposterior diameter of the chest. We believe that more accuracy and reproducibility might be gained by measuring the diameter by bony and therefore relatively more constant landmarks on the lateral Bucky chest roentgenogram. Accordingly the anteroposterior diameter of the chest was measured at its widest portion on the film along a horizontal line extending from the inner surface of the angles of the ribs posteriorly to the inner surface of the sternum anteriorly. This line as a rule passed through the lower portion of the hilus of the lung. (Fig. 3.) The diameter measurements were reproducible to 0.1 cm.

Areas of disease were determined by simply tracing their outlines—if sufficiently circumscribed and definite—with the planimeter. (Fig. 2D.) Pole-within-circle planimetry was necessary to measure the area of the lung fields; areas of cardiomediastinum or disease were amenable, being smaller, to pole-outside-circle measurement.

ROUTINE CHEST ROENTGENOGRAM TECHNIC

	Distance	Milliampere-seconds	Average KV	Other
Postero-anterior	6 feet	5	74	.....
Lateral	6 feet	120	77	Potter-Bucky grid

FIG. 1.

The (modified) radiological chest volume (RCV_1) was derived by multiplying the value in square centimeters for the "area of the lung fields" by the distance in centimeters for the anteroposterior diameter of the chest obtained from the lateral chest film; cardiomediastinum and disease volumes were obtained in like manner by multiplying their respective area values by the anteroposterior diameter of the chest. "Radiological total lung capacity" is determined from the RCV_1 by the use of the regression equation to be described.

The polar planimeter is so constructed that the measuring wheel which rolls along the film surface is located at some distance from the tracing point. The lung fields fill most of a routine 14 by 17 inch chest film; this often causes the wheel of the planimeter to pass beyond the confines of the film at several points when pole-within-circle measurement of lung field area is done. If the wheel passes from one level to another, as over a lap joint between two pieces of paper or films, or from one type of surface texture to another, or over any joint that is not a smooth butt joint between two surfaces of the same and uniform texture, the reading of the instrument is thrown off appreciably. It was thus necessary, in order to achieve accurate results, to construct an oversize viewbox on which to measure the films. This box consisted of a piece of frosted plate glass measuring 26 by 29 inches placed on suitable supports, with a light source of two fluorescent lamps beneath. Old pieces of x-ray film were glued to the glass so that an aperture 14 by 17 inches was left in the

* Compensating Polar Planimeter, Model 4236M. Keuffel and Esser Co., Hoboken, N. J.

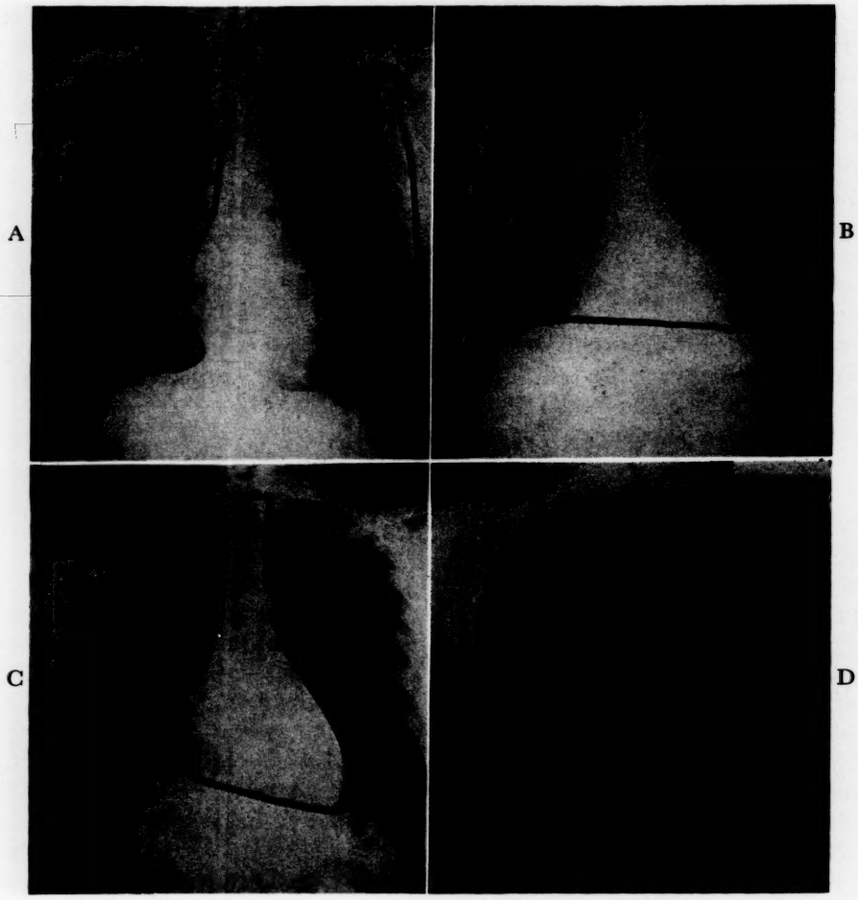

FIG. 2. Technics for planimetric measurement of postero-anterior chest roentgenograms; A, lung field areas as suggested by Binger and Brow; B, "area of lung fields" measured by Hurtado and Fray and the authors; C, authors' technic of measuring area of heart and mediastinum; D, authors' technic of measuring areas of disease (as might be produced by a right-sided empyema and a left-sided upper lobe abscess).

center. A film to be measured is placed in this nicely fitting rectangle which has borders of one-film thickness and provides a smooth butt-joint all around. This device gives a foot-wide space of similar texture and height all around the film to be measured and can be constructed with a minimum of expense. (Fig. 4.)

The original radiological chest volume as determined by Hurtado and Fray is termed RCV; our modifications are termed RCV_1, RCV_2, RCV_3 and RCV_4.

RESULTS

Three of the four modified radiological chest volumes determined for each patient are listed in the three columns farthest to the right in Table II. To form these three columns the whole series of seventy-six patients was studied three times, forming the modified RCV in a somewhat different way each time, to determine just which technic of radiological measurement might be most accurate. First, the RCV_1 was determined for all. Secondly, what we have called the RCV_2 was determined, as follows, for the whole series: for those patients having no measurable type of disease, their RCV_2 figures were entered in the RCV_1 column; for those subjects possessing measurable pathologic areas on their postero-anterior roentgenograms, the volume of the disease was calculated by multiplying its area by the anteroposterior diameter of the chest, and this volume subtracted from the RCV_1 figure previously calculated for these diseased subjects, the difference being entered in the RCV_2 column as the RCV_2. Thus given a series of

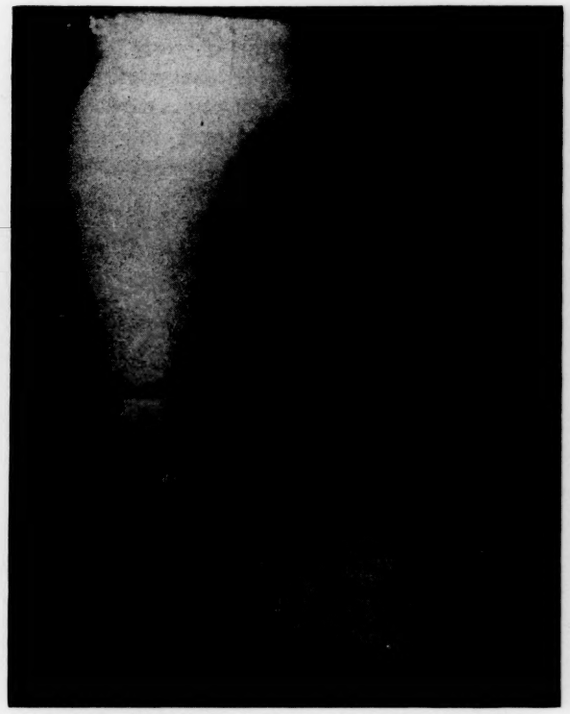

FIG. 3. Technic for determining anteroposterior chest diameter on lateral film.

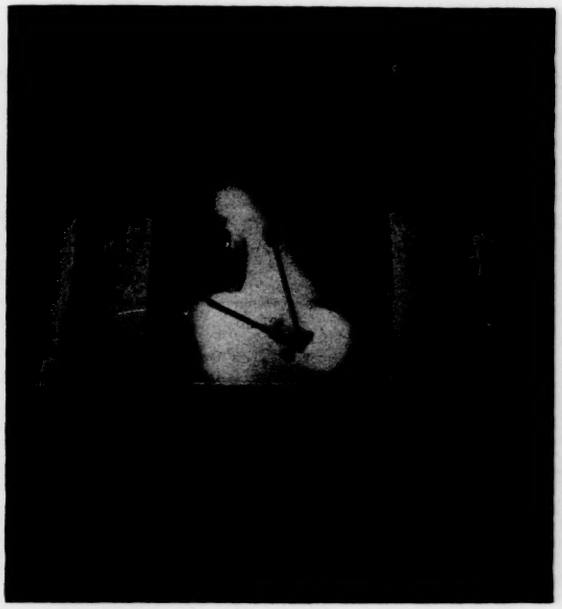

FIG. 4. Oversize viewbox with instrument in position for pole-outside-circle planimetry.

subjects, some diseased and some not diseased, it may be determined whether accuracy of RCV_1 estimation is to be increased or decreased for the series as a whole by subtracting the radiological volume of disease from the RCV_1 values of those patients possessing measurable disease masses. Thirdly, the radiological volume of the heart and mediastinum was determined for each case by the technic described previously. This volume was subtracted from the RCV_1 value, the difference (RCV_3) being entered in the RCV_3 column. Thus it may be determined whether correlation between gaseous and radiological measurement of total lung capacity is increased or decreased by subtracting the radiological volume of the heart and mediastinum from the RCV_1 value.

Table III compares the technics just described statistically. Group I in Table III presents the relationships between total lung capacity determined "physiologically" and the RCV_1; group II the correlation exhibited by RCV_2. In group III of Table III the RCV_4 is considered. This was obtained by subtracting the radiological volume of the heart and mediastinum from the RCV_2 of each case. Thus the RCV_4 tests the effect of subtracting radiological volumes of *both* pathologic masses and the heart and mediastinum from the plain RCV_1.

Table III contains two additional groups, IV and V. RCV_1 only was determined for both these groups. Group IV is composed of the thirty-three patients possessing a type of disease *not* including replacement of lung parenchyma by *masses* of non-ventilating tissue. Seventeen of these patients had diffuse emphysema; one had asthma and bronchitis; two exhibited pectus excavatum; one was believed to have a functional disorder; twelve subjects had previously undergone either lobectomy or pneumonectomy and were thought to be free of parenchyma-replacing disease masses in the lung tissue remaining. (In determining RCV_1 on patients with one lung, only the translucent area was traced with the planimeter.) Group V includes the remaining forty-three of the seventy-six patients—those who had types of disease which included some element of replacement of ventilating pulmonary tissue by diseased material. The disease of each patient is noted in Table II. Representative diseases in this group are tuberculosis, bronchiectasis and bronchogenic carcinoma.

Given one type of pulmonary disease, e.g., bronchogenic carcinoma, it will be understood that pathologic change differing in both nature and extent may be present in different subjects, for example a segmental atelectasis in one case and a diffusely widened mediastinum in another.

While the specific variation taken by the pathologic process in each case is not stated in Table II, whenever an area of disease sufficiently discrete to be outlined with the planimeter was present the radiological volume of the process was measured. Those patients possessing measurable areas of density on their postero-anterior chest films may be identified by an entry in the column of Table II headed "RCV_1 minus radiological volume of disease." A small number of cases possessed replacement of lung tissue so diffuse or of such a nature (as a widened mediastinum or elevated hemidiaphragm) as to make measurement impossible; these subjects are located exclusively in the group with disease masses (group V, Table III) and are identified by asterisks after their RCV_1 values in Table II.

In Table II the subjects are presented as

TABLE III

ANALYSIS OF CORRELATIONS BETWEEN TOTAL LUNG CAPACITY AND VARIOUS MODIFICATIONS OF RADIOLOGICAL CHEST VOLUME

		Groups (Full Descriptions in Text)				
		I	II	III	IV	V
		Total Capacity Correlated with:				
		RCV_1	RCV_2	RCV_4	RCV_1	RCV_1
		Whole Series of Patients			Patients without Disease Masses	Patients with Disease Masses
Total cases in group		76	76	76	33	43
Per cent of males		68.4	68.4	68.4	72.7	65.1
Case numbers		1–76	1–76	1–76	1–21 53–64	65–76 22–52
Age, years	Mean S.D. Range	44.14 ±16.389 7–70	44.14 ±16.389 7–70	44.14 ±16.389 7–70	45.21 ±10.929 7–69	43.33 ±12.177 8–70
Total capacity, liters	Mean S.D. Range	4.69 ±1.408 1.87–8.22	4.69 ±1.408 1.87–8.22	4.69 ±1.408 1.87–8.22	4.89 ±1.589 1.87–7.87	4.54 ±1.227 2.07–8.22
Radiological chest volume, liters	Mean S.D. Range	12.68 ±4.806 1.86–26.10	12.40 ±4.716 1.86–25.29	8.80 ±3.475 1.86–20.82	12.14 ±5.669 1.86–23.45	13.09 ±3.967 4.21–26.10
Coefficient of correlation	r S.E. of r	+0.709 ±0.115	+0.791 ±0.115	+0.665 ±0.115	+0.906 ±0.177	+0.526 ±0.154
Coefficient of determination		0.503	0.626	0.429	0.821	0.277
Z transformation	Z S.E. of Z Z S.E. of Z	+0.885 ±0.177 7.564	+1.074 ±0.177 9.179	+0.784 ±0.177 6.701	+1.505 ±0.182 8.269	+0.585 ±0.158 3.703
P between pairs		>5%	>5%		<1%	

individuals; in Table III this individuality has been lost, the patients being presented in the groups I–V described previously. The total number of cases and the male-female distribution in each of the five groups are given. In the third horizontal column down in Table III the individuals from Table II are identified by number groupings. The means for age, total lung capacity and radiological chest volume are given for each group, with standard deviation (S.D.) from the mean and the range of values encountered for each entity in each group.

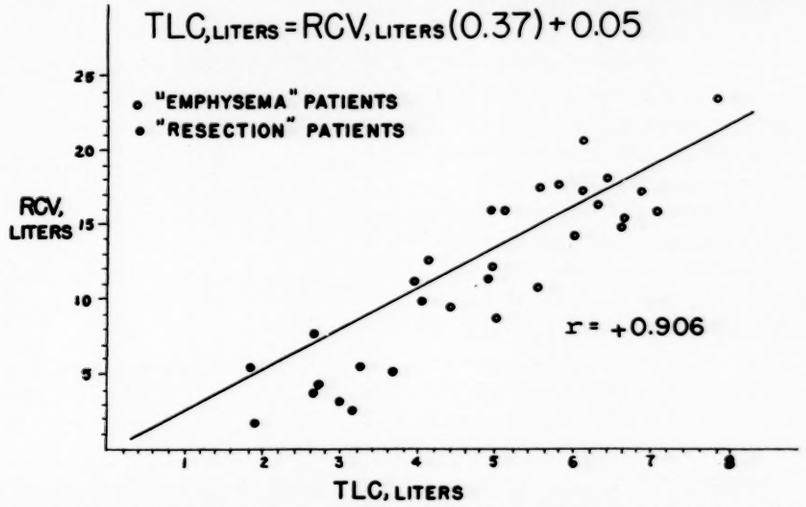

FIG. 5. Scatter diagram, Group 5. The correlation between total lung capacity and modified radiologic chest volume (RCV_1).

Continuing downward in Table III, correlation between total lung capacity and RCV in each group is analyzed statistically. The coefficients of correlation (r) with the standard error (S.E.) for each r are presented, followed by the coefficient of determination (r^2) for each group. The coefficient of determination is considered to express the proportion of the total amount of variation accounted for by the relationship between RCV and total lung capacity shown by r. In other words, formation of r^2 enables one to estimate the proportion or percentage of the variance ($S.D.^2$) of one variable that is associated with the variance of another variable.[24]

The Z transformation is performed for each group. This transforms r into a measure the sampling distribution of which is approximately normal and enables one to test the difference between correlation coefficients of two series.[11] The standard error (S.E.) of each Z is also provided, with the ratio $\frac{Z}{\text{S.E. of } Z}$ in each case.

At the bottom of Table III, P (probability) values are calculated for certain *pairs* of groups, testing the significance of the *difference* between two Z values, and not the significance of r or Z values as they stand alone. Groups I, II and II_I are not independent, having one array (the total lung capacity) common to all three; groups IV and V are mutually independent, being composed of two different groups of subjects. Accordingly, when the P values between pairs for groups I and II, and for groups II and III are calculated, their mutual lack of independence must be taken into consideration; the P between the Z values for groups IV and V may be derived by the rather simpler calculations for two independent series.

DISCUSSION

In group I, in which RCV_1 was compared with total lung capacity (the RCV_1 including the radiological volumes of the heart and mediastinum and any diseased areas), the coefficient of correlation (r) obtained was $+0.709 \pm 0.115$.* When for those cases with measurable areas of disease on their films the radiological volume of the disease was subtracted from the total, and the whole series again studied (RCV_2), r was $+0.791 \pm 0.115$.* The probability (P), however, that this difference arose from the workings of chance is greater than 5 per cent.† Still and all this is suggestive that the accuracy of radiological lung capacity determination is

* Standard error.

† P derived from Z test.

increased by subtracting radiological volumes of disease on the chest roentgenograms.

When the radiological volume of the heart and mediastinum is subtracted from the RCV_2 of each case in group II, and the resulting radiological volumes (group III, RCV_4) compared with the total lung capacities for all seventy-six cases, r decreases to $+0.655 \pm 0.115$.* This is suggestive that accuracy of radiological lung capacity measurement is decreased if cardiomediastinal volume is subtracted from RCV_1. Again, however, the difference observed may likely have been due to chance as P between the two Z values is greater than 5 per cent.

In group IV, in which only patients without parenchyma-replacing disease masses are considered, the correlation between RCV_1 and total capacity possesses the high coefficient (r) of $+0.906 \pm 0.177$.* Figure 5 presents the scatter diagram for this relationship, from which it will be seen that the value of r is illustrated by the tendency of the individual values to cluster about the regression line.

The r obtained when those patients with parenchyma-replacing disease are considered separately (group V) has the lowest value of the study, $+0.526 \pm 0.154$.* The value of the P between the Z values of groups IV and V shows the difference between them to be significant, indicating that a real discrepancy exists by which degree of departure from a healthy state could be estimated by comparing the RCV with the total lung capacity as determined by one of the gas dilution or lung washout methods. Further, the correlation in "health" (i.e., a state wherein ventilating parenchyma is not replaced by disease masses) between volumetric measurements from routine chest roentgenograms and total lung capacities is rather greater than any previously observed between the total capacity and physical measurements, and slightly greater (although probably not significantly so statistically) than the correlations obtained by previous investigators between total lung capacities and radiological chest volumes determined from specially taken chest films with coaching of the subject.

As volumetric measurements of routine films have not been performed on sufficient numbers of normal subjects, and as vital capacity and the other subdivisions of total capacity could not be derived from routine films in any case, it seems advisable to us to employ values of *both* the Kaltreider-Baldwin and radiological chest volume types to compare with the value determined by gaseous methods in attempting to evaluate just how much of the lung parenchyma of the individual subject is not in a functional state at the time of the examination.

* Standard error.

USE OF RADIOLOGICAL TOTAL LUNG CAPACITY WITH SPIROMETRY IN DETERMINATION OF $\frac{\text{RESIDUAL VOLUME}}{\text{TOTAL LUNG CAPACITY}} \times 100$ RATIOS

The regression equation was calculated for the relationship observed in group IV of Table III, and its form is:

$$\text{Total lung capacity, liters} = RCV_1, \text{ liters } (0.37) + 0.05.$$

As this equation was derived from the data of those subjects free of *masses* of non-ventilating diseased tissue, we believe it may be considered to represent an adequate equation for the relationship between lung washout and radiological lung capacity values in a "control" series, although emphysema, the disease occurring most frequently in the group, is not a healthy state. True controls have previously been established by other investigators for the validity of the radiological chest volume concept in healthy subjects. The patients from whose data the presiding equation was derived may be considered to form a control series when patients with varied types of pulmonary volume changes are considered; a control series in the sense that non-ventilating disease masses are absent and localized areas of pathologic change are not apparent on the chest roentgenogram.

Table IV compares total capacity determined in the customary way, by a combination of spirometry and an open circuit lung washout procedure, with total capacity determined from the routine chest films by subjecting the RCV_2 values for each subject to the regression equation derived from the "control" series. Residual volume is then determined in two ways by subtracting the observed vital capacity value, obtained by spirometry, from these two total capacity figures for each subject. The

$$\frac{\text{residual volume}}{\text{total lung capacity}} \times 100 \text{ ratios}$$

are then calculated for each type of determination. Lastly, the deviation of the "radiological"

TABLE IV

RADIOLOGICAL-SPIROMETRIC VERSUS LUNG WASHOUT-SPIROMETRIC DETERMINATION OF $\frac{\text{RESIDUAL VOLUME}}{\text{TOTAL LUNG CAPACITY}} \times 100$ RATIOS

Case No.	Total Lung Capacity Determined by a Combination of Spirometry and Open-Circuit Nitrogen Washout			Vital Capacity (L.)	Total Lung Capacity Calculated from RCV_2 (from Volumetric Measurements of Routine Postero-anterior and Lateral Chest Roentgenograms)				Departure of Radiological from Gaseous $\frac{RV}{TLC} \times 100$ Ratio, Absolute % Difference	Diagnosis
	Total Lung Capacity (L.)	Residual Volume (L.)	$\frac{RV}{TLC} \times 100$ (%)		Radiological Chest Volume (RCV_2) (L.)	Total Lung Capacity (L.)	Residual Volume (L.)	$\frac{RV}{TLC} \times 100$ (%)		
1	6.40	4.30	67	2.10	17.26	6.43	4.33	67	0	Emphysema
2	6.17	3.87	63	2.30	17.49	6.52	4.22	65	+2	Emphysema
3	6.95	5.80	83	1.15	17.47	6.51	5.36	82	−1	Emphysema
4	6.48	3.68	57	2.80	18.37	6.84	4.04	59	+2	Emphysema
5	6.63	3.73	56	2.90	14.70	5.49	2.59	47	−9	Emphysema
6	6.61	4.77	72	1.84	15.42	5.76	3.92	68	−4	Emphysema
7	4.42	1.62	37	2.80	9.56	3.59	0.79	22	−15	Asthma, bronchitis
8	6.03	3.73	62	2.30	14.41	5.39	3.09	57	−5	Emphysema
9	5.82	2.73	47	3.09	17.79	6.63	3.54	53	+6	Emphysema
10	7.87	5.62	71	2.25	23.45	8.73	6.48	74	+3	Emphysema
11	6.15	4.09	67	2.06	20.76	7.73	5.67	73	+6	Emphysema
12	3.98	2.48	62	1.50	11.11	4.16	2.66	64	+2	Emphysema
13	5.56	3.41	61	2.15	17.71	6.61	4.46	68	+7	Emphysema
14	5.15	3.30	64	1.85	16.12	6.02	4.17	69	+5	Emphysema
15	5.17	3.13	61	2.04	14.13	5.28	3.24	61	0	Emphysema
16	7.09	2.17	31	4.92	15.95	5.95	1.03	17	−14	Emphysema
17	6.34	3.52	56	2.82	16.49	6.15	3.33	54	−2	Emphysema
18	4.13	2.83	69	1.30	12.71	4.75	3.45	73	+4	Emphysema
19	5.02	1.17	23	3.85	8.88	3.33	<0	..	....	Functional disorder
20	4.98	2.20	44	2.78	12.20	4.56	1.78	39	−5	Pectus excavatum
21	5.56	1.82	33	3.74	10.88	4.07	0.33	8	−25	Pectus excavatum
22	6.24	1.81	29	4.43	14.62	5.46	1.03	19	−10	Bronchiectasis
23	4.19	1.79	43	2.40	25.59*	9.51	7.11	75	+32	Bronchiectasis
24	5.16	2.64	51	2.52	13.72	5.13	2.61	51	0	Bronchiectasis
25	3.34	0.80	24	2.54	11.75	4.40	1.86	42	+18	Bronchiectasis
26	5.29	1.69	32	3.60	12.59	4.71	1.11	24	−8	Bronchiectasis
27	4.11	2.16	53	1.95	10.12	3.79	1.84	49	−4	Bronchiectasis
28	2.99	0.77	26	2.22	7.54	2.84	0.62	22	−4	Bronchiectasis
29	4.54	1.14	25	3.40	9.66	3.62	0.22	6	−19	Bronchiectasis
30	3.94	1.59	40	2.35	9.37	3.50	1.15	33	−7	Bronchiectasis
31	4.29	1.37	32	2.92	10.61	3.98	1.06	27	−5	Bronchiectasis
32	4.49	2.84	63	1.65	12.67	4.73	3.08	65	+2	Bronchiectasis
33	3.65	1.38	38	2.27	8.47	3.18	0.91	29	−9	Bronchiectasis
34	5.90	2.72	46	3.18	13.80	5.16	1.98	38	−8	Bronchogenic carcinoma
35	5.35	1.83	34	3.52	12.96*	4.84	1.32	27	−7	Bronchogenic carcinoma
36	3.28	0.78	24	2.50	17.55	6.55	4.05	62	+38	Bronchogenic carcinoma
37	4.86	2.19	45	2.67	11.18*	4.18	1.51	36	−9	Bronchogenic carcinoma
38	4.03	2.32	58	1.71	12.62	4.72	3.01	64	+6	Bronchogenic carcinoma
39	6.00	2.10	35	3.90	15.81	5.90	2.00	34	−1	Bronchogenic carcinoma
40	4.90	2.88	59	2.02	15.30	5.71	3.69	65	+6	Bronchogenic carcinoma
41	2.96	2.01	68	0.95	9.99*	3.74	2.79	75	+7	Bronchogenic carcinoma
42	5.30	2.50	47	2.80	17.12†	6.39	3.59	56	+9	Bronchogenic carcinoma
43	5.07	2.77	55	2.30	11.89†	4.45	2.15	48	−7	Bronchogenic carcinoma
44	5.29	3.09	58	2.20	15.65	5.84	3.64	62	+4	Bronchogenic carcinoma
45	4.51	1.41	31	3.10	8.34†	3.13	0.03	1	−30	Pulmonary tuberculosis
46	2.86	1.20	42	1.66	9.23†	3.47	1.81	52	+10	Pulmonary tuberculosis
47	3.73	1.33	36	2.40	9.24†	3.47	1.07	31	−5	Pulmonary tuberculosis
48	5.29	2.10	40	3.19	13.27*	4.96	1.80	36	−4	Pulmonary tuberculosis
49	4.68	2.10	45	2.58	14.31†	5.34	2.76	52	+7	Pulmonary tuberculosis
50	5.22	1.82	35	3.40	10.70*	4.01	0.61	15	−20	Pulmonary tuberculosis
51	8.22	5.49	67	2.73	18.90†	7.05	4.32	61	−6	Pulmonary tuberculosis
52	5.18	0.99	19	4.19	13.63†	5.09	0.90	18	−1	Pulmonary tuberculosis
53	2.69	0.78	29	1.91	7.73	2.91	1.00	34	+5	Lobectomy
54	4.92	2.12	43	2.80	11.58	4.33	1.53	35	−8	Lobectomy
55	4.97	2.37	48	2.60	16.18	6.03	3.43	57	+9	Lobectomy
56	3.25	1.05	32	2.20	5.55	2.10	<0	..	....	Lobectomy
57	2.70	1.63	60	1.07	4.02	1.54	0.47	31	−29	Pneumonectomy
58	1.87	0.72	39	1.15	1.86	0.65	<0	..	....	Pneumonectomy
59	3.00	1.55	52	1.45	3.21	1.24	<0	..	....	Pneumonectomy
60	4.04	1.14	28	2.90	10.00	3.75	0.85	23	−5	Lobectomy
61	1.88	0.62	30	1.26	5.37	2.04	0.78	38	+8	Pneumonectomy
62	3.67	0.97	26	2.70	5.16	1.96	<0	..	....	Pneumonectomy
63	3.14	1.64	52	1.50	2.84	1.09	<0	..	....	Pneumonectomy
64	2.66	1.09	41	1.57	4.34	1.65	0.08	5	−36	Pneumonectomy
65	5.19	3.14	61	2.05	10.47*	3.92	1.87	48	−13	Pneumonitis with cyst
66	5.48	2.28	42	3.20	20.11*	7.49	4.29	57	+15	Abscess
67	2.25	1.43	64	0.82	8.21	3.09	2.27	73	+9	Widened mediastinum
68	5.54	4.30	78	1.22	13.88*	5.19	3.97	77	−1	Emphysema with blebs
69	3.47	2.30	66	1.17	18.23*	6.79	5.62	83	+17	Cysts, pneumonitis
70	5.54	1.58	29	3.96	14.16*	5.29	1.33	25	−4	Spontaneous pneumothorax
71	2.07	1.28	62	0.79	4.21†	1.61	0.82	51	−11	Fibrocystic disease
72	5.40	2.08	38	3.32	14.12*	5.28	1.96	37	−1	Pneumonitis
73	5.97	1.48	25	4.49	11.28*	4.22	<0	..	....	Actinomycosis
74	3.30	1.36	41	1.94	10.94	4.10	2.16	53	+12	Esophageal carcinoma
75	2.10	1.03	49	1.07	8.34	3.13	2.06	66	+17	Chest deformity, cor pulmonale
76	3.87	1.62	42	2.25	10.55*	3.95	1.70	43	+1	Abscess

* Radiological volume of discrete diseased area has been subtracted.
† Disease present but not amenable to measurement.

from the "gaseous" $\frac{RV}{TLC} \times 100$ ratio is presented for each case.

Table v analyzes the departures of the radiological from the gaseous ratios, breaking down the series into groups of patients with similar diseases. When those patients possessing pulmonary emphysema exclusively were considered, the $\frac{RV}{TLC} \times 100$ ratios determined radiologically and spirometrically were within ± 10 units of the ratios for the same patients determined by lung washout and spirometry in 94.1 per cent of the cases, within ± 7 units in 88.2 per cent, and within ± 5 units in 70.6 per cent. Only 5.9 per cent of the patients with emphysema demonstrated a departure of the radiological from the gaseous ratio of more than ± 10 units.

Total lung capacities determined from the routine chest films of the patients with bronchogenic carcinoma, subtracting radiological volumes of diseased areas when present, demonstrated an agreement almost as good when residual volume percentages were calculated. In this type of disease 90.9 per cent of the cases had agreement between the residual volume fractions of ± 10 units or less, while 63.6 per cent agreed within ± 7 units, and 9.1 per cent disagreed by more than ± 10 units.

The agreement between residual volume percentages for those groups of patients with tuberculosis and miscellaneous chest diseases was very poor, as might have been inferred from the value of the correlation coefficient determined previously for patients possessing this type of disease.

The residual volume percentages for those patients who had undergone either pneumonectomy or lobectomy were also poor. It is ventured that compensatory rather than emphysematous overinflation, with lung hernias, may be responsible in part for this discrepancy.

It is thought that in cases in which there is not a diffuse and extensive replacement of lung parenchyma by disease, the correlations between the lung capacity determined radiologically and that determined conventionally are great enough perhaps to permit the use of radiologic measurement of routine chest roentgenograms as a rapid and inexpensive screening method for determination of total lung capacity, with an error little greater than the more tedious and expensive gaseous methods. Total capacity determined radiologically might then be used with the vital capacity quickly found with a

TABLE V

ACCURACY OF RADIOLOGICAL-SPIROMETRIC DETERMINATION OF $\frac{\text{Residual Volume}}{\text{Total Lung Capacity}} \times 100$ Ratios

	Total Cases in Disease Grouping	Case No.	Per cent of Cases in Disease Groupings for Which Radiological and Gaseous Ratios Agree within Specified Number of Ratio Units				
			Difference Greater than ±10 Units (%)	Difference ±10 Units or Less (%)	Difference ±7 Units or Less (%)	Difference ±5 Units or Less (%)	Difference ±3 Units or Less (%)
"Emphysema" group	17	1–6 8–18	5.9	94.1	88.2	70.6	47.1
"Carcinoma" group	11	34–44	9.1	90.9	63.6	18.2	9.1
"Tuberculosis" group	8	45–52	25.0	75.0	62.5	37.5	12.5
"Resection" group	12	53–64	58.4	41.6	16.7	16.7	0
"Miscellaneous" group	16	7, 19–21, 65–76	62.5	37.5	31.2	31.2	18.8
Whole series	76	1–76	31.6	68.4	52.6	38.2	19.7

simple spirometer as a screening method rapidly to examine large numbers of individuals for increase in the per cent of total lung capacity occupied by the residual volume. Cases found outside the normal range by this method, and cases demonstrating diseased areas on their films, might then be referred for more complete study with determination of their pulmonary volumina by more conventional technics. It probably would increase accuracy, in cases with discretely measurable areas of disease, to calculate the RCV_2; that is, to subtract the radiological volume of the pathologic change from the total RCV_1 before comparison and calculation of compartment ratios.

It seems from the degree of correlation obtained that routine chest films are more reproducible than previously supposed, and that special films with or without spirometric checking of completeness of inspiration are not needed, as long as the chest films demonstrate the subject to have been in a reasonably complete state of inspiration when the pictures were taken. In the Department of Radiology at Albany Hospital, for example, the routine instruction given to all patients about to have a chest film (after positioning) is "take a deep breath and hold it, please." It will be recalled that in only one of seventy-seven patients was the chest film so obtained frankly not in full inspiration. No more instruction than this appears necessary. Our regression equation should be equally applicable when postero-anterior and lateral chest films taken elsewhere with the same standard technic are measured. It is believed that increased accuracy in radiological determination of total lung capacity is obtained by measurement of the anteroposterior diameter of the chest between bony landmarks on the lateral film, rather than externally with calipers at an inconstant level as done previously.

SUMMARY

In a group of seventy-six patients with various types of pulmonary disease, values for total lung capacity determined by volumetric measurement of routine postero-anterior and lateral chest roentgenograms were compared with the total lung capacities determined by spirometry and an open circuit method of determining functional residual capacity. Comparisons and correlations were analyzed statistically.

The method used to estimate radiological chest volume (RCV) was that of Hurtado and Fray with two modifications: (1) the anteroposterior chest diameter was measured between bony landmarks on a lateral chest film, rather than externally at an inconstant level with calipers; (2) routine rather than special films were used. The radiological total lung capacity may be calculated from the modified RCV by the regression equation derived.

High degrees of correlation were obtained, and evidence suggested that accuracy of radiological total lung capacity determination was increased by subtracting the radiological volume of regions of disease on the x-ray films, and decreased by subtracting the radiological volume of the heart and mediastinum from the total RCV. Lung field area on routine chest roentgenograms seems more constant than was previously supposed.

When the subjects were separated into two groups, one consisting of thirty-three patients in whom the disease present did not include replacement of ventilating lung tissue, the other comprising forty-three patients with types of disease often replacing lung tissue with masses of non-functioning material, a large and statistically significant difference in correlation between RCV and total lung capacity was found for the two groups. It is believed that this difference enables degree of replacement of functioning pulmonary tissue in the single subject to be estimated more quantitatively than by previously available methods.

The closeness of correlation between radiological and gaseous methods of lung capacity determination in the group of subjects possessing volumetrically intact pulmonary tissue was sufficient to suggest soundness and feasibility in screening large numbers of individuals for abnormal changes in pulmonary compartment ratios by a combination of simple spirometry and radiological measurement of *routine* chest roentgenograms. In seventeen patients with pulmonary emphysema the $\frac{\text{residual volume}}{\text{total lung capacity}} \times 100$ ratios determined using radiological and lung washout total capacities agreed within ± 10 units in 94.1 per cent of cases, and within ± 5 units in 70.6 per cent. Agreement was poor in diseases with mass replacement of ventilating parenchyma.

Accuracy in RCV calculation is believed to be increased by measuring the anteroposterior chest diameter radiologically rather than externally with calipers. As a standard routine

chest x-ray technic was used, the regression equation derived here for radiological determination of total lung capacity may be used in other hospitals employing the same roentgenographic technic.

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The Ventilatory Effects of the Head-Down Position in Pulmonary Emphysema*

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INABILITY of the diaphragm to ascend during expiration, due to impairment of lung elasticity, has been in part counteracted by pneumoperitoneum[1] and by the use of abdominal belts.[2–5] Increased diaphragmatic excursion was obtained by these methods of elevating the intra-abdominal pressure. Breathing exercises to aid diaphragmatic movement have long been advocated.[6,7] Heckscher[8] proposed a posture-correcting treatment, including easy standing position and elevating the thorax above the head, as a surer method of developing abdominal respiration than breathing exercises. A training program to facilitate the practice of diaphragmatic breathing was described by Barach[9,10] as one of the most valuable of the physical aids to relieve dyspnea on exertion in these cases. Although abdominal breathing was at first taught in the supine position, observation of patients tilted head down at an angle between 12 and 20 degrees during the procedure of exsufflation made it clear that visceral pressure on the diaphragm was an effective method of instituting diaphragmatic breathing in these subjects.[11] Relief of dyspnea was marked and accompanied by conspicuous decrease in the effort of breathing and prompt abandonment of the use of the upper intercostals and accessory neck muscles of respiration. The weight of the abdominal organs elevated the diaphragm in a manner comparable to pneumoperitoneum and the application of abdominal belts.[12] Observations were then made of the effect of tilting the patient head down on pulmonary ventilation, blood gases and pH.

METHODS

The pulmonary ventilation during the inhalation of air and 100 per cent oxygen was recorded by means of Reichert attachment to the Collins spirometer. The oxygen concentration was kept constant during the inhalation of air by (1) admitting oxygen through a rotameter type of flow meter equal to the oxygen consumption of the individual, or (2) the use of a leveling device attached to the Collins spirometer which automatically delivers the amount of oxygen consumed by the patient.[13] The spirometric graph was kept level with these methods during inhalation of air and oxygen. The method of Van Slyke and Neil was employed for determination of the oxygen and CO_2 contents of arterial blood; the pH was measured by the Beckman pH meter.

The patient was tilted at the angle that clinically appeared to be most effective in the relief of dyspnea, between 12 and 20 degrees: in most instances an incline of 16 degrees was used. A pillow was placed under the head to reduce flushing of the face. Observations were made on the pulmonary ventilation, breathing air and 100 per cent oxygen in the sitting position and breathing air in the supine and head-down position. The order of the test was reversed in half of the patients. The ventilation was measured during the latter half of a forty-five-minute test period, following which arterial blood was drawn for determination of blood gases and pH.

RESULTS

The results of varying the posture of the patient on the pulmonary ventilation are shown in Table 1. The average decrease in pulmonary ventilation of twenty-four cases when oxygen was substituted for air was 15 per cent. The average decrease in ventilation in this group breathing air in the head-down posture, as compared to the sitting position, was 22 per cent. In the first ten cases there was an average decrease of 14 per cent when the pulmonary ven-

* From the Department of Medicine, Columbia College of Physicians and Surgeons, and the Presbyterian Hospital, New York, N. Y. The support of this study was aided by grants from the National Foundation for Infantile Paralysis and the Mary W. Harriman Fund.

tilation was recorded in the supine position as compared to the sitting position.

The effect of the head-down position during the inhalation of air on the blood gases of ten patients is shown in Table II. The average decrease in pulmonary ventilation resulting from the head-down position in this group was 26 per cent. In one patient in whom clinical evidence of right- and left-sided heart failure was present, the arterial oxygen saturation decreased 1.6 volumes per cent. In three more cases the arterial oxygen saturation did not vary more than plus or minus 2 per cent. The remaining six patients manifested an increase in arterial oxygen saturation in the head-down as compared to the sitting position, i.e., 3.0, 3.1, 3.6, 4.4, 8.0 and 8.3 volumes per cent.

In seven of ten cases no significant change in pH took place in the head-down position. In two cases a fall in pH occurred, from 7.50 to 7.45 and 7.43 to 7.39, with an increase in pCO_2 of 4 and 5 mm. Hg, respectively. In one patient with respiratory acidosis the pH rose from 7.27 to 7.44 with a decrease in pCO_2 of 35 mm. Hg, and a rise in arterial oxygen saturation from 83.4 to 87.0 volumes per cent. The changes in blood gases and pH in the individual cases are shown graphically in Figure 1.

In fifteen patients the degree of diaphragmatic excursion during quiet breathing was estimated during fluoroscopy when tilting the patient between 12 and 18 degrees; the average descent of the right leaf of the diaphragm during inspiration was approximately 3.5 cm. In the

TABLE I

PULMONARY VENTILATION IN PATIENTS WITH PULMONARY EMPHYSEMA

Case No.	Pulmonary Ventilation						
	Sitting			Head Down 16°		Supine	
	Sitting Air (cc./min.)	100% Oxygen (cc./min.)	Per cent Change, Air to Oxygen	Air (cc./min.)	Per cent Change, Air Sitting to Air Head Down	Air (cc./min.)	Per cent Change, Air Sitting to Air Supine
1	12,150	9,520	−21.6	8,150	−32.9	9,380	−22.8
2	9,890	7,040	−28.8	5,980	−35.5	7,310	−26.1
3	6,140	4,970	−19.1	4,910	−20.0	5,010	−18.4
4	9,930	7,640	−23.1	7,500	−24.5	7,940	−20.0
5	6,680	6,680	0.0	5,910	−11.5	6,430	− 3.7
6	9,720	9,880	+ 1.6	8,100	−16.7	9,460	− 2.7
7	7,750	7,000	− 9.7	6,860	−11.5	6,990	− 9.8
8	10,900	9,950	− 8.7	9,480	−13.0	10,730	− 1.6
9	8,410	6,680	−20.6	5,730	−31.9	5,910	−29.7
10	8,630	8,140	− 5.7	7,690	−10.9	7,840	− 9.2
11	12,350	9,360	−24.2	9,480	−23.2		
12	14,580	13,130	− 9.5	11,630	−20.2		
13	10,520	10,800	+ 2.7	8,490	−19.3		
14	8,760	7,210	−17.7	5,980	−31.7		
15	10,340	8,230	−20.4	8,180	−20.9		
16	8,130	6,540	−19.6	6,710	−17.5		
17	13,750	11,550	−16.0	11,150	−18.8		
18	7,000	5,020	−28.2	6,030	−13.9		
19	9,100	7,250	−20.4	7,630	−16.2		
20	13,200	11,100	−16.0	8,990	−32.7		
21	9,400	9,590	+ 1.8	7,620	−18.9		
22	10,700	9,000	−16.0	6,940	−35.2		
23	6,120	4,270	−30.2	3,700	−49.5		
24	12,030	10,400	−14.0	10,130	−15.9		
Average			−15.1		−22.3		
Average of first ten cases			−13.5		−20.8		−14.4

standing posture these cases manifested either no descent of the diaphragm or a slight downward movement, invariably less than 1.5 cm. Roentgenograms were made in a number of patients in the standing and supine positions at the end of inspiration and expiration, but patient and the presence or absence of left ventricular failure.

COMMENTS

In the six patients in whom a significant rise in arterial oxygen saturation took place in the

TABLE II

EFFECT OF "VISCERO-DIAPHRAGMATIC" BREATHING IN THE HEAD-DOWN POSITION ON PULMONARY VENTILATION, OXYGEN SATURATION, pCO_2 AND pH OF TEN PATIENTS WITH PULMONARY EMPHYSEMA

Case No.	Pulmonary Ventilation			Oxygen Saturation Volumes Per cent			CO_2 Tension (pCO_2)			pH		
	Sitting (cc./min.)	Head Down (cc./min.)	Change %	Sitting	Head Down	Change	Sitting (mm./Hg)	Head Down (mm./Hg)	Change (mm./Hg)	Sitting	Head Down	Change
1	9,100	7,630	−16	93.0	96.0	+3.0	46.0	46.0	0	7.47	7.46	−0.01
2	9,890	5,980	−40	67.7	76.0	+8.3	43.0	43.0	0	7.51	7.51	0
3	7,550	5,500	−27	94.2	94.0	−0.2	36.0	38.0	+2	7.48	7.48	0
4	11,450	8,510	−26	90.0	88.4	−1.6	40.0	40.0	0	7.49	7.48	−0.01
5	12,400	9,850	−21	94.4	95.7	+1.3	32.0	38.0	0	7.48	7.48	0
6	10,880	7,500	−31	94.5	97.6	+3.1	36.0	38.0	+2	7.52	7.52	0
7	10,200	8,430	−17	91.8	96.2	+4.4	41.0	40.0	−1	7.48	7.49	+0.01
8	10,200	8,110	−20	97.3	96.4	−0.9	39.0	43.0	+4	7.50	7.45	−0.05
9	8,220	5,750	−30	93.0	101.0	+8.0	44.0	49.0	+5	7.43	7.39	−0.04
10	13,910	9,620	−31	83.4	87.0	+3.6	70.0	45.0	−35	7.27	7.44	+0.17
Average			−26			+2.9			−2			+0.01

accurate timing of the completion of the respiratory cycle was manifestly difficult of attainment. By a special mechanical device Wade and Gilson[13] were able to obtain simultaneous records of diaphragmatic movement and spirometric tracings; in normal individuals tilted head down 45 degrees a rise of 6 cm. in the resting level of the diaphragm related to the iliac crest was observed, but total diaphragmatic excursion was not increased. In one patient in whom careful measurements were made, x-rays in deep inspiration and expiration revealed a progressive increase in diaphragmatic movement as the patient was tilted from the standing to the supine and head-down positions. As seen in Table III the right anterior leaf of the diaphragm descended during deep inspiration 15 cm. standing, 2.4 cm. supine and 4.0 cm. tilted head down 16 degrees. Similar results are shown by measurements of the left anterior and left posterior leaves of the diaphragm. A variety of factors are involved in the optimal tilt required for maximal diaphragmatic excursion, including the weight of the abdominal contents, the degree of atrophy of the diaphragmatic muscle, psychologic response of the head-down position the diminished pulmonary ventilation could perhaps be explained by the decrease in anoxia resulting from improved alveolar ventilation incident to increased diaphragmatic excursion. The evidence for more efficient exchange of gases, even with a striking diminution of the minute volume of ventilation, was indicated by the maintenance of a relatively constant pH and pCO_2 in five of six of these cases. In the sixth case (No. 9, Table II) there was a rise in pCO_2 from 44 to 49 and a fall in pH from 7.43 to 7.39, suggesting in this instance that the diminished pulmonary ventilation was accompanied by some CO_2 retention. In the patient with respiratory acidosis the rise in pH was remarkable, from 7.27 to 7.44. This response seems similar to the favorable results from pneumoperitoneum in the treatment of pulmonary emphysema with carbon dioxide acidosis,[14] which presumably may also be explained by increased diaphragmatic excursion.

In four cases in which little or no change took place in the arterial oxygen saturation the decrease in pulmonary ventilation may be explained, as in the previous group, by better ventilation and perfusion, factors in emphysema

that have recently been subjected to careful study.[16] It is interesting that the same degree of anoxia did not stimulate ventilation to the extent that was present with costal breathing in the sitting position. The anoxic ventilatory drive was unchanged; nor was there significant

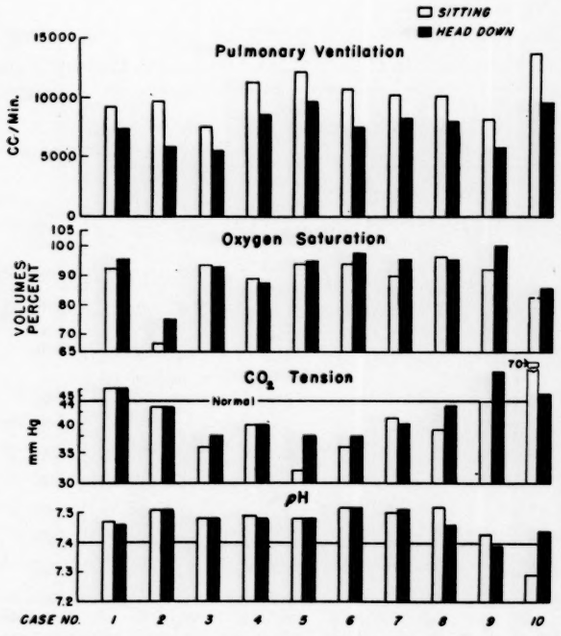

FIG. 1. Pulmonary ventilation and blood gas changes in pulmonary emphysema after tilting to the head-down position.

alteration of the pH or pCO_2 except in one case (No. 8, Table II) in which the pH fell from 7.50 to 7.45.

Other factors which should be considered as possible explanations for the decrease in the head-down position include the following: increasing the blood pressure in the carotid sinus and aortic arch may increase inhibitory reflexes to the respiratory center and decrease respiration.[15] An increase in cerebral blood flow tends to decrease the volume of breathing.[16] Changes in the Hering-Breuer reflex, with a shift of considerable volume of blood to the lungs and temporary vascular congestion, may be involved; however, these latter conditions appear to increase the respiratory ventilation: in normal individuals tilted from the horizontal to the 75 degree head-up position an immediate although transient *decrease* in minute volume of breathing was found.[17]

The changes in breathing pattern when the patient with pulmonary emphysema is tilted head down are shown in Figure 2. Diaphragmatic descent is shown by abdominal protrusion

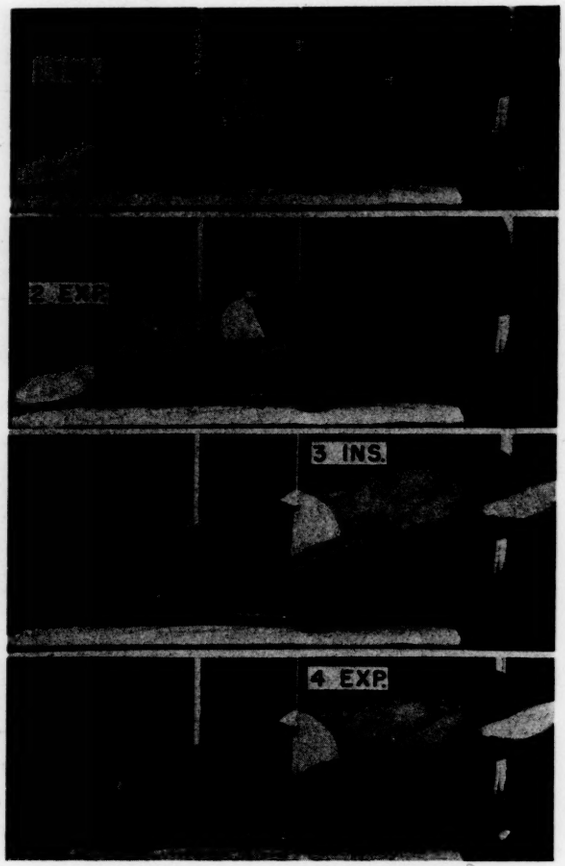

FIG. 2. Effect of head-down position on breathing pattern. During inspiration with the patient tilted head downward, the diaphragmatic contraction results in protrusion of the abdomen. During expiration (2) the abdomen becomes scaphoid as the diaphragm is elevated partly by the pressure of the viscera and partly as the result of the conscious contraction of the abdominal muscles. When the patient is tilted with the head up, inspiration (3) takes place as a result of contraction of the intercostal muscles with at times raising of the chest upward and forward as a result of the accessory muscles in the neck and paradoxic elevation of the diaphragm. During expiration (4) with the head tilted upward thoracic volume is decreased as the inspiratory musculature relaxes and the diaphragm may become lowered as a consequence of the cessation of the previously developed negative intrapleural pressure of the inspiratory cycle. After training, however, the patients in whom diaphragmatic respirations have developed are able to abandon paradoxic diaphragmatic movement and manifest abdominal protrusion during inspiration even during the head-up position. The abdomen becomes flattened during expiration due to the previously developed negative intrapleural pressure accomplished by diaphragmatic contraction and in some cases by deliberate contraction of the abdominal wall.

during inspection when the head-down position is assumed. The untrained patient tilted head up may raise the chest, with paradoxic elevation of the diaphragm during inspiration, a circumstance that accounts for inefficient ventilation of the lower lobes of the lungs.

TABLE III
DIAPHRAGMATIC EXCURSION IN A PATIENT WITH PULMONARY EMPHYSEMA IN THE STANDING, SUPINE AND HEAD-DOWN POSITIONS

Position	Right Anterior Leaf (cm.)	Left Anterior Leaf (cm.)	Left Posterior Leaf (cm.)
Standing	1.5	2.7	3.2
Supine	2.4	4.2	3.2
Head down 16°	4.0	6.5	4.0

The marked fall in ventilation associated with increased diaphragmatic breathing due to tilting is obviously responsible for clinical relief of dyspnea, even though no parallel alteration in blood gases was found in four cases without acidosis. The fact that oxygen and carbon dioxide diffusion was maintained in three of these four cases with one-fourth less minute volume of respiration indicates clearly that absorption of oxygen and elimination of CO_2 was facilitated by the induced diaphragmatic breathing, as against the previously predominantly costal breathing. The decreased ventilation produced by inhalation of 100 per cent oxygen is characteristically accompanied by CO_2 retention and acid shift in pH, as recently reviewed by Richards[18] and Bickerman and Beck;[19] these findings are in marked contrast to the response induced in most cases of emphysema when visceral pressure elevates the diaphragm approximately 3.5 cm.

The patients with pulmonary emphysema in whom the arterial oxygen saturation was unchanged in the head-down position have apparently become adapted to their accustomed anoxia to such an extent as to permit a 20 to 25 per cent reduction in their previous breathing requirement. The hyperventilation which is characteristic of the sitting position seems to be related to the inefficiency of costal respiration as well as a response to arterial anoxia, since it is relieved by inhalation of 100 per cent oxygen. When the head-down position induced "viscero-diaphragmatic" respiration, it was indeed surprising to find that the same degree of anoxia no longer produced hyperventilation. The most tenable thesis to explain this response appears to be the adaptation to anoxia which is maintained at the same degree with net gain of relief of dyspnea. Were the lowered ventilation solely due to reflex factors, impairment of CO_2 elimination and respiratory acidosis should have become manifest. The reverse was indeed true in one case with carbon dioxide acidosis. Furthermore, in another patient with pulmonary emphysema and respiratory insufficiency the head-down position induced diaphragmatic breathing and was then employed continuously for three days, associated with immediate relief of dyspnea, even though oxygen administered at 3 L. per minute through a nasal catheter had not improved the previous gasping type breathing with the upper intercostals and neck muscles.

The clinical use of viscero-diaphragmatic breathing, especially as part of the training program designed to develop abdominal respiration in patients with pulmonary emphysema, is described elsewhere.[11,20,21]

SUMMARY

Observations were made on the effect of visceral elevation of the diaphragm produced by the head-down position in patients with pulmonary emphysema. Striking relief of dyspnea was accompanied by increased diaphragmatic excursion and a marked decrease in the minute volume of ventilation. In twenty-four subjects the average decrease in pulmonary ventilation on tilting from the sitting to the head-down posture was 22 per cent. The average decrease in pulmonary ventilation for this group in the sitting position, when 100 per cent oxygen was substituted for air, was 15 per cent.

The arterial oxygen saturation was measured in the lying head-down position after forty-five minutes; in one case with associated cardiac insufficiency a fall of 1.6 volumes per cent took place; in three more cases there was no significant change; in six cases the arterial oxygen saturation increased.

In seven of ten patients in whom an average fall of 26 per cent in pulmonary ventilation took place with the head-down position the pH and pCO_2 showed little or no change. In two cases a rise in pCO_2 of 4 and 5 mm. Hg was found, with a fall in pH from 7.43 to 7.39

and from 7.50 to 7.45. In one patient with an associated respiratory acidosis the pH rose markedly, from 7.27 to 7.44.

The effect of elevation of the diaphragm by upward pressure of the viscera resulted in increased diaphragmatic excursion, comparable in some respects to raising the resting level of the diaphragm by increase of the intra-abdominal pressure through the use of abdominal belts or by pneumoperitoneum. The increased efficiency of alveolar ventilation of the lower lobes induced by diaphragmatic as compared to costal breathing was illustrated by the blood gas changes in eight of ten subjects tested.

In three cases in which the arterial oxygen saturation was unchanged there appeared to be adaptation to an accustomed degree of anoxia which permitted marked lowering of pulmonary ventilation and consequent relief of dypsnea.

These observations provide a physiologic basis for the clinical use of viscero-diaphragmatic breathing in patients with pulmonary emphysema.

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Tic of the Respiratory Muscles*

Report of Three Cases and Review of Literature

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TIC of the respiratory muscles aside from singultus is rare. The spastic movements† may involve all or part of the diaphragm. When the contractions are sufficiently rapid, the disturbance is often referred to as diaphragmatic flutter. One case which has been repeatedly reported in the American literature has attained national fame.[1–6]

Another group of respiratory disturbance is represented by tic of the intercostal muscles. It is even rarer than tic of the diaphragm. It produces a striking clinical picture which has been described in the German literature[7–9] as "see-saw movement of the thoracic wall of noncardiac origin" or as "pseudopulsations."[10]

This report presents three cases of tic of the respiratory muscles. Two of the cases are diaphragmatic flutter-fibrillation and one is tic of intercostal muscles. A discussion of these interesting disturbances based on our cases and others reviewed from the literature will be presented. Singultus has not been included in this study.

FLUTTER-FIBRILLATION OF THE DIAPHRAGM

CASE I. (Hosp. No. X 4039.) S. D., a thirty-six year old married female, was admitted on February 7, 1952, because of respiratory distress. The patient had had similar attacks previously. The first episode was in 1937 when she was three months' pregnant. For the subsequent three years she was free of these episodes. From 1940 to 1943 these attacks recurred, averaging once yearly, and varying in severity. In 1943, following a therapeutic abortion and sterilization, the attacks became more frequent and were followed by marked weakness. Most of the attacks started at night. On three occasions they were sufficiently severe to require hospitalization.

At the age of six the patient had rheumatic fever with carditis. During the ensuing years her physical activities were practically unrestricted. At the age of eight the patient had scarlet fever. In 1940 she was hospitalized twice for nephrolithiasis and pyelitis. Two years later she was hospitalized for pneumonia. There were two uneventful pregnancies. A third pregnancy in 1943 was interrupted because of heart and kidney disease. Because of the presence of ankle edema at that time the patient was advised to use digitalis which she took at irregular intervals. She occasionally received injections of mercurials, the last one three days prior to admission.

On the day of admission the patient complained of severe headache accompanied by weakness. She retired early but was suddenly awakened with respiratory distress. Her breathing was deep and rapid and was accompanied by a boring substernal pain. There were occasional deep gasps after which the chest pain subsided. After the spell had lasted for forty-five minutes the patient, while on the way to the bathroom, collapsed, and an ambulance was called. The ambulance physician found the patient in a state of severe respiratory distress. She was shaking and her body was arched posteriorly in an effort to breathe. Spasmodic breathing alternated with periods of apnea lasting up to twenty-five seconds. Oxygen was given and aminophyllin was administered intravenously. Certain findings, however, contrasted with the severe respiratory distress. The lungs were clear. The heart rate was 90/minute, and the heart rhythm was regular. When questioned as to how she felt the patient would answer with a smile that she was all right. On admission the

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† Differentiation of tic and clonic spasm is not always feasible;[26] the terms are used interchangeably here as elsewhere in the literature.

FIG. 1A. Case 1. Epigastric pulsations are shown recorded during sleep when the quivering movements of diaphragmatic tic were absent. The pulsations are in the rhythm of the heart beat as is demonstrated by the electrocardiogram.

resident physician expressed the suspicion that the attack was of hysteric nature.

Physically the patient was well developed and well nourished. Occasionally she showed grimacing and posturing. Her breathing was deep and rapid, the respiratory rate varying from 35 to 64/minute. There was no cyanosis. At times the patient made a deep gasp. Periods of hyperpnea alternated with apnea. The cervical veins were not distended. The lungs were clear.

The apical thrust of the heart was not palpable. A slight heaving pulsation was felt during systole in the fourth and fifth intercostal spaces. No abnormal dullness was noted on percussion of the sternum or in the second left interspace. Marked dullness was present in the third left interspace, extending from the sternum for a distance of about 4 cm. Auscultation in the apical area revealed a snapping first sound, a presystolic murmur and an early diastolic rumble. The second pulmonic sound was loud and reduplicated. The heart rhythm was regular. The rate was 72/minute. The blood pressure was 120/70 mm. Hg. The liver and spleen were not enlarged. There was no peripheral edema. Neurological findings were negative. The temperature was normal.

Urinalysis, blood count, blood sugar, serum electrolytes including chlorides, sodium and CO_2 combining power, were normal. The sedimentation rate (Wintrobe) was 22 mm./hour initially, and subsequently 14 mm./hour. The venous pressure in the arm was 100 mm. H_2O and remained unchanged on hepatic pressure. The arm to tongue circulation time (decholin) was 14 seconds. Roentgen study revealed an enlarged heart of "mitral configuration" and displacement of the esophagus by a dilated left atrium. The pulmonary vascular markings were not accentuated. The electrocardiogram showed digitalis effect and premature atrial beats.

During her hospital stay respiratory disturbances were accompanied by complaints of weakness and anorexia. There were bouts of severe vomiting. Digitalis was discontinued on the fourth hospital day without adverse effect to the patient. Psychiatric interviews confirmed the impression of emotional imbalance and psychiatric treatment was advised.

Bouts of hyperventilation continued. On February 17, 1952, the patient was examined by one of us (W. D.) for evaluation of the cardiac status. She was not hyperventilating. At that time rapid, irregular vibrations, which were much faster than the heart rate, were noted in the epigastric area. Simultanuously, rapid movements of the anterior thoracic wall were observed, which were especially pronounced on the right side and seemed to be opposite in direction to the "pulsations" of the epigastrium. The rate of the vibrations was approximately 120/minute. Every once in a while the fast movements were interrupted by a deep, sighing breath. The patient did not seem to be in distress, in contrast to the episodes of hyperventilation which were associated with a boring subcostal pain. At times the rate of the vibrations rose to 200/minute and more. It was suspected that flutter of the diaphragm was present. Fluoroscopy revealed that the left half of the diaphragm was high and immobile while the right half exhibited rapid oscillations. When fluoroscopy was repeated the next day, both halves of the diaphragm moved rapidly at a rate of approximately 130/minute; however, the excursions were larger on the right than on the left side. The rate of the diaphragmatic oscillations varied greatly even while the patient was observed at fluoroscopy. When she was asked to take a deep breath, she was not always able to respond; when she did, the diaphragm exhibited symmetrical respiratory excursions of less than normal amplitude. At the peak of inspiration the size of the rapid oscillations appeared diminished.

Vibrations of the epigastrium and thoracic wall persisted for many days, exhibiting marked variations in both the rate and amplitude of the excursions. Episodes of hyperventilation became

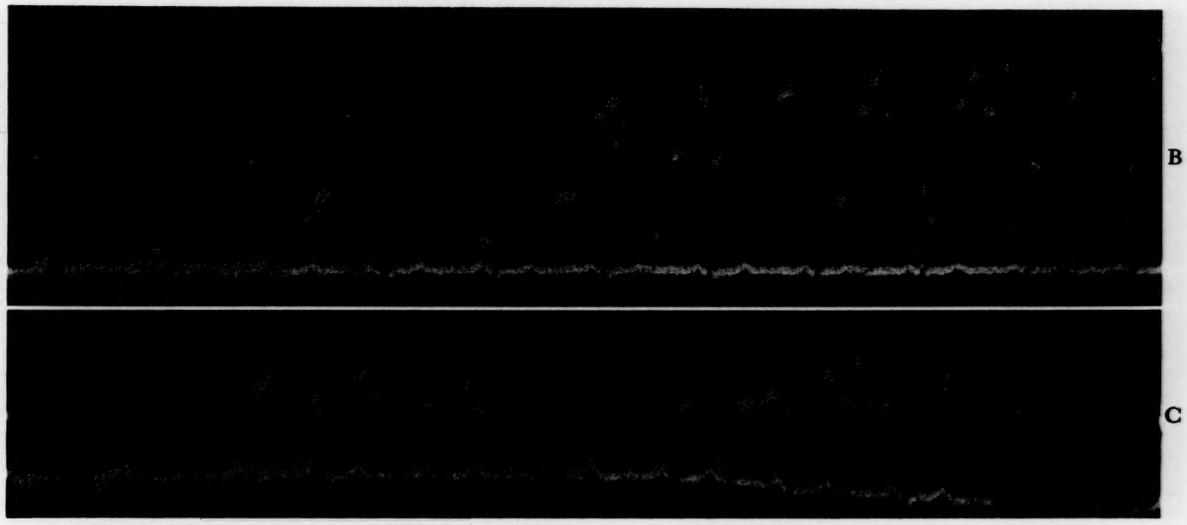

FIG. 1. B, after awakening of the patient. The epigastric pulsations are masked by large and small oscillations which are independent of the cardiac rhythm. Their rate is 170/min. C, record of epigastric vibrations obtained on February 24, 1952. Steep peaks are present which occur in rapid, irregular sequence, obviously independent of the heart beat. The rate of the vibrations is 300/min.

less frequent. Subsequently both the attacks of hyperventilation and the quivering movements in the epigastric area subsided, and the patient was discharged on March 3, 1952. The final diagnosis was: (1) Diaphragmatic flutter-fibrillation; the vibrations of the chest wall were thought to be secondary to the movements of the diaphragm; (2) tight mitral stenosis, well compensated.

Graphic records of the vibratory movements of the epigastrium and chest wall were repeatedly taken in the cardiographic department, using the Cambridge mechanical transducer. An attempt was made to obtain a control record of the pulsations in the epigastrium in the absence of vibratory movements. On February 22, 1952, a record of the epigastric pulsations was made while the patient was asleep and the quivering movements stopped. Figure 1A shows epigastric pulsations which, as can be seen from the simultaneously recorded electrocardiogram, are synchronous with the cardiac cycle. The tracing shows the usual systolic depression* which is preceded by a high peak caused by atrial systole. The atrial wave is accentuated because of the presence of mitral stenosis. A few smaller peaks are apparently due to movements of the heart which are transmitted through the diaphragm to the epigastrium.

* The systolic depression in the epigastric area is due partly to the diminution in the volume of the heart, and partly to aspiration of blood from the liver into the thorax during systole.

FIG. 1D. Record of movements of the chest wall, with the receiver in the third intercostal space in the right mid-clavicular line. Broad oscillations of unequal amplitude, contour and spacing are noted, which are independent of the heart action.

Figure 1B was taken immediately after the patient awakened, when the epigastric vibrations returned. The pattern of epigastric pulsations, as shown in Figure 1A, is now masked by rapid, large and small oscillations, which clearly have no relationship to the cardiac cycle. The rate of the oscillations is approximately 170/minute.

Figure 1C shows a record of the epigastric vibrations which was obtained on February 24, 1952. A rapid sequence of steep peaks is noted; the rate is approximately 300/minute. The oscillations are irregular in amplitude and spacing but exhibit greater regularity than in Figure 1B. It is obvious that they bear no relationship to the cardiac cycle.

Figure 1D shows a record of the movements of the chest wall taken on February 17, 1952. The receiver was in the third intercostal space

in the right mid-clavicular line. Broad oscillations of unequal amplitude and spacing are noted which are not related to the cardiac cycle. The rate of the oscillations is approximately 130/minute.

Case II. (Hospital No. X 4995.) G. W., a forty year old woman, was admitted on March 23, 1952, because of severe dyspnea. At the age of ten she had rheumatic fever. Six years later exertional dyspnea developed. When the patient was eighteen she complained of severe substernal pain when doing heavy lifting. There were several bouts of epistaxis. The patient was then informed that she had rheumatic heart disease. At the age of twenty-five she was hospitalized for seven weeks because subacute bacterial endocarditis was suspected. Digitalis therapy was instituted at that time. In 1950 paroxysmal nocturnal dyspnea developed. The patient became orthopneic and required bed rest almost continuously. Administration of mercurials was started three months prior to admission.

The patient was hospitalized on various occasions for conditions other than her heart ailment: in 1918 for tonsillectomy; in 1926 for appendectomy; in April, 1951, for pneumonia, and in December, 1951, for a genitourinary infection. A vibratory movement in the epigastrium was first noted in 1949 and had persisted since with short interruptions. The disturbance was diagnosed as diaphragmatic flutter. It was severe enough to require hospitalization in 1949 and 1951.

Physical examination revealed a severely ill woman of frail body build. The cervical veins were distended and exhibited a "double pulse" which was demonstrated by graphs to consist of a high *a* wave at an early *v* wave. Scattered moist rales were audible over the pulmonary bases. The heart was markedly enlarged. The apical thrust was felt in the seventh intercostal space 1 inch inside the left anterior axillary line. There were systolic and presystolic murmurs at the apex. A diastolic blow was heard at Erb's point. The second pulmonic sound was accentuated. The heart rhythm was regular at a rate of 92/minute. The blood pressure was 150/70 mm. Hg. The liver was markedly enlarged, prominent and hard. It extended slightly below the umbilical line.

Respiration was irregular. Normal breathing alternated with periods of hyperventilation, during which the respiratory rate varied from 44 to 56/minute. Rapid, deep breathing was followed by respiratory standstill. On such occasions rapid, irregular vibrations of rather large amplitude appeared in the epigastric area. The chest wall did not participate in these movements. The vibrations occurred in "spasms," notably when the patient was in the supine position, and they usually ceased during walking. Epigastric tremor often followed episodes of hyperventilation. The latter occurred usually when the patient was tense or excited. Hyperventilation disappeared when the attention of the patient was diverted.

There was 3+ albuminuria; otherwise the urinary findings were normal. The blood count was normal. The hematocrit was 56. The erythrocyte sedimentation rate was 3 mm/hour. The cephalin flocculation test was negative. Thymol turbidity was 6.6 units. Icteric index was 14. Mazzini test was negative. The venous pressure in the arm was 240 mm. H_2O, and rose to 360 mm. after pressure in the hepatic area. The arm to tongue (decholin) circulation time was twenty-two seconds. Roentgen study revealed an enlarged heart of "mitral configuration." The left ventricle seemed to participate in the enlargement. The electrocardiogram showed right axis deviation and signs suggestive of atrial enlargement.

Records of the epigastric movement were taken with a Cambridge mechanical transducer. The first tracing was obtained while the patient held her breath. (Fig. 2A.) It showed pulsations of the epigastrium which conformed to the cardiac cycle. There were atrial waves and a sharp systolic depression. In addition, a number of small peaks were noted, apparently caused by movements of the heart which were transmitted through the diaphragm.

Figure 2B demonstrates hyperventilation which followed the enforced standstill of breathing. The large excursions of deep breathing do not entirely obscure the pulsatory movements.

Figure 2C (which is continuous with B) shows termination of hyperventilation which is apparently followed by a period of apnea. Large, irregular oscillations are noted which obviously have no relationship to the heart action and obscure the pulsatory movements. The rate of the vibrations is approximately 270/minute.

Figure 2D (continuous with B and C) again shows rapid oscillations which are irregular in spacing and amplitude.

Figure 2E was obtained immediately after D.

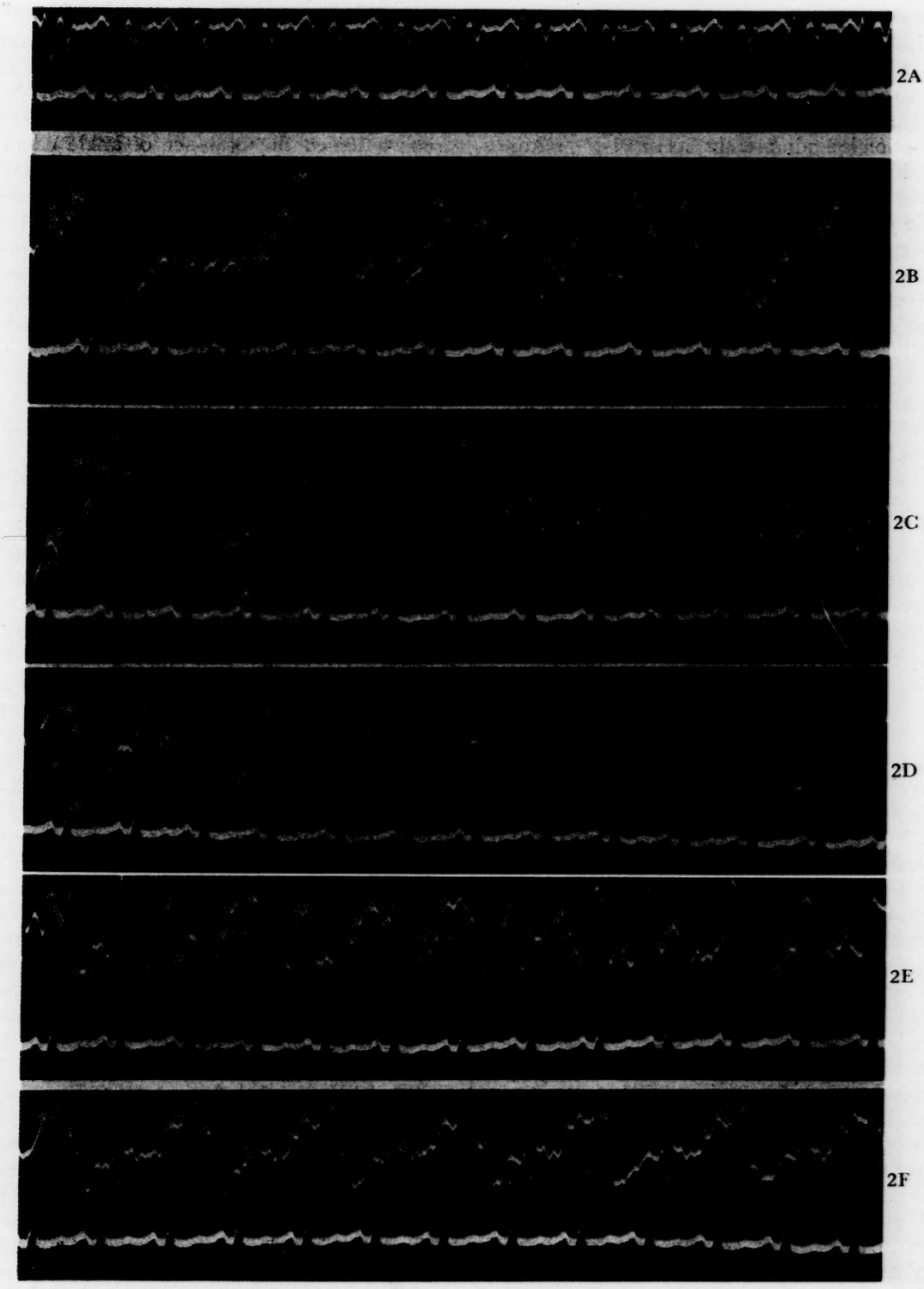

FIG. 2. Case II. A, record of epigastric pulsations, taken while the patient held her breath. The pulsations conform to the cardiaccy cle as is shown by the electrocardiogram. B, large excursions due to hyperventilation distort but do not mask entirely the pulsatory movements. C, (continuous with B) hyperventilation is still seen in the first part of the tracing. It is followed by apnea, during which large, irregular oscillations occur independently of the heart beat; their rate is 270/min. D, (continuous with C) rapid oscillations are seen as in C, irregular in spacing, contour and amplitude. E, (tracing obtained soon after D) the rate of the irregular vibrations has slowed down to 150/min. The epigastric pulsations are no longer completely masked. F, (tracing obtained immediately after E) the irregular vibrations have ceased. Hyperventilation is present again. Regular pulsations of the epigastrium are discernible which conform to the cardiac cycle.

The rate of the irregular epigastric oscillations has slowed down to approximately 150/minute so that pulsatory waves are again discernible.

Figure 2F was obtained immediately after E. Epigastric vibrations have subsided. Hyperventilation is again present; its rate is 50/minute. Pulsations of the epigastrium conforming to the cardiac cycle are distinctly recognizable.

The clinical diagnosis was: Rheumatic heart disease; tight mitral stenosis; aortic regurgitation; congestive heart failure; flutter-fibrillation of the diagram.

During her hospital stay the patient was afebrile; she remained dyspneic and orthopneic. On March 25, 1952, she became suddenly cyanotic and her dyspnea increased. The heart rate was rapid and irregular. The electrocardiogram showed atrial flutter-fibrillation. Peripheral vascular collapse associated with pulmonary edema developed. Tenderness in the area of the left leg was noted. The patient was treated with cedilanid, aminophyllin and potassium chloride. Her condition deteriorated rapidly and death occurred on March 27th, four days after admission. Permission for postmortem examination was not obtained.

TIC OF THE INTERCOSTAL MUSCLES

CASE III.* L. T., a thirty-one year old female nurse, was admitted in June, 1930, because of complaints of palpitation, shortness of breath and precordial pain. There was no history of rheumatic fever or chorea. Since the age of twelve the patient had frequent attacks of tonsillitis. At the age of seventeen an attack of tonsillitis was followed by acute glomerulonephritis. The patient was hospitalized for three and one-half years. At that time she began to complain of palpitation, shortness of breath and pain in the precordium. Because of the severe precordial pain she used morphine and became an addict to the drug. Tonsillectomy was performed at twenty-seven years of age. The condition of the patient improved so that she could return to work. Two years later palpitation and fever returned. The patient was hospitalized and endocarditis was diagnosed. After three months she returned to work but shortly thereafter suffered a relapse. She was again hospitalized and a thorough study failed to reveal evidence of organic heart disease. Fever was indicated by axillary measurements but not by rectum. In 1929 the patient had a cholecystectomy. She was again hospitalized in 1930 because of ankle edema. (However, the hospital report denied the presence of ankle edema or any other evidence of congestive heart failure. The patient was diagnosed a "severely neurotic" person.)

Physical examination revealed a pale woman of slender body build. She was not cyanotic or dyspneic. The cervical veins were not congested. The lungs were clear. The liver was not enlarged. There was no pitting edema.

On inspection of the anterior thoracic wall a forceful and extensive pulsation was noted. The sternum, especially the manubrium and the adjoining clavicular and infraclavicular areas, appeared to protrude rhythmically with each systole. A diagnosis of aortic aneurysm was made. However, fluoroscopy failed to show dilatation of the aorta. Moreover, when the pulsation of the chest wall was timed with the radial pulse it was recognized that the propulsive movement coincided with diastole, and that the middle and upper thoracic portions were pulled in during systole. Simultaneously with the retraction of the chest wall a broad, heaving apical thrust was felt in the fifth intercostal space in the left midclavicular line, suggesting marked enlargement of the left ventricle. However, attempts to delineate a circumscribed apex beat failed. Wherever the palpating finger was placed in the neighborhood of the "apex beat" the same vigorous protrusion and hardening of the intercostal tissue was felt, from the fourth rib down to the costal arch and laterally to the left axillary area. This diffuse propulsive movement, which was synchronous with the retraction of the middle and upper thoracic portions, gave the impression of a see-saw movement of the anterior thoracic wall.

Percussion revealed a normal cardiac dullness. On auscultation a peculiar bruit was heard which sounded close to the ear and was synchronous with the heart beat. It was present not only in the precordial area but extended to the lower left portions of the anterior chest wall close to the costal arch. X-ray study revealed a cardiac silhouette of normal size and shape. All other clinical and laboratory findings were normal.

Because of the observation of a diffuse systolic retraction of the chest wall adhesive pericarditis

* The case has been reported previously by one of the writers (W. D.[10]); it is identical with the second case reported by Holler.[9]

was considered as a possible cause. However, there was no evidence to support this diagnosis. The enormous pulsation of the chest wall, which contrasted with normal findings on percussion and x-ray, indeed presented what the observer of the first case of this type had termed "a physical-diagnostic puzzle."[7] After a prolonged period of observation it was noted that the intensity of the pulsatory movements varied at different times. By means of graphic registration it was revealed that, on occasion, the "pulsation" of the chest wall was not synchronous with the peripheral pulse. Moreover, when morphine was withheld and manifestations of abstinence developed the movements of the chest ceased altogether and the peculiar superficial murmurs disappeared. Both phenomena returned when morphine was again administered. We concluded that, as in the cases previously reported,[7,8] muscular contractions of the thoracic wall rather than the action of the heart were responsible for both the movements of the chest wall and the bruits.

COMMENTS

Incidence and Distribution. In addition to the three patients reported here, seventeen cases of tic of the respiratory muscles recorded in the literature were reviewed. The total of twenty cases comprises seventeen instances of diaphragmatic spasm and three cases of tic of the intercostal muscles. Singultus was not included in this study.

The age ranged from nine months to eighty-four years. The incidence of respiratory tic was equal for males and females.

Rate. The rate of the spastic movements ranged from 60 to 300/minute. The higher rates of 200 to 300/minute were observed only in instances of spasm of the diaphragm.[1–5,13,15] Such high rates justify the term diaphragmatic flutter. In tic of the intercostal muscles the frequency of the contractions was usually less than 100/minute and was often identical with the heart rate. On occasions the rate rose above 100/minute when the movements of the chest wall became faster than the heart action.[7] In both types of respiratory tic the rate varied within a wide range not only from patient to patient but even daily in the same patient. In one instance variations in the rate of diaphragmatic contractions from 100 to 300/minute were noted on different occasions.[1]

Rhythm. The rhythm of the spastic contractions was regular only in a minority of cases, notably when the movements of the chest wall or diaphragm were synchronous with, and apparently controlled by, the heart action.[7–9,16,24] Even then a tendency to irregularity was noticeable on prolonged observation. In our Cases I and II diaphragmatic tic was grossly irregular both in spacing and amplitude of the contraction. One observer, in describing a case of diaphragmatic spasm, spoke of an "erratic respiratory disturbance."[24] When the irregularity is marked and the rate sufficiently rapid, the term diaphragmatic flutter-fibrillation describes more adequately this type of respiratory tic.

Amplitude and Force. The amplitude of the excursions and the force of the spastic contractions were subject to considerable variations even in the same patient. Frequently the size of the diaphragmatic excursions, as viewed by fluoroscopy, ranged from 5 to 10 mm.[1,4,5] In one instance[11] the upward and downward oscillations of the diaphragm measured approximately 6 inches in amplitude. Some observers have stressed the great force of the diaphragmatic contractions by which the chest was jolted and jerky movements were transmitted to the heart, stomach and intestines.[14,22] In a case of left-sided spasm of the diaphragm which was synchronous with the heart action the "pulsations" in the left upper quadrant were forceful enough to cause suspicion of a dissecting aneurysm.[16] Similarly, in two instances of tic of the intercostal muscles the vigorous movements of the chest wall gave rise to a diagnosis of aortic aneurysm and marked enlargement of the heart.

Extent of Muscular Involvement. The degree of involvement of muscles varied in different cases. In twelve patients with diaphragmatic tic fluoroscopy revealed the spastic contractions to be bilateral in eight and unilateral in four. In one patient (our Case I) both unilateral and bilateral spasms of the diaphragm were observed on successive days. When both halves of the diaphragm were involved, the right leaf occasionally showed larger excursions than the left.[5,23] In two patients in whom the tic was synchronous with and apparently caused by the heart action only the left half of the diaphragm was affected.[16,25] In one instance the flutter movements were confined to a small area of the right leaf of the diaphragm.[18] Sometimes, as in our Case I, the vibrations of the epigastrium spread to the chest. This was interpreted as a

secondary movement caused by tic of the diaphragm.

When tic of the intercostal muscles was present, most of the anterior thoracic wall was involved, the middle and upper portions being pulled in while the left lower region (and occasionally the symmetrical area on the right side) bulged forward. The simultaneous excursions in opposite direction resulted in a see-saw movement of the chest wall. In one instance the movements of the thoracic wall were accompanied by small vibrations of the diaphragm which were interpreted as secondary movements.[8]

Relation of Diaphragmatic Tic to Normal Respiration. Normal respiratory excursions of the diaphragm were demonstrated by fluoroscopy in the presence of tic of the intercostal muscles[8] and in instances of diaphragmatic spasm.[1,4,18,22] In the latter, fluoroscopy showed rapid oscillations superimposed on normal respiratory excursions of the diaphragm. In other cases of diaphragmatic tic normal respiration was absent[12,14,15,17] but returned promptly when the tic was relieved by blockage of the phrenic nerves. Cessation of normal breathing was attributed to hyperventilation resulting from the rapid, spasmodic contractions of the diaphragm. It was believed that normal stimuli for respiration were lacking because of excessive blowing off of carbon dioxide which caused a shift of the blood pH toward the alkaline side.[14] In our Cases I and II records of the epigastric vibrations taken during attacks of diaphragmatic tic failed to demonstrate the diaphragmatic excursions of normal respiration.

Associated Tics. Some patients also exhibited, in addition to diaphragmatic spasm, tic of the facial muscles, extremities and body,[13,24] or hiccough.[23]

Clinical Features. Pain in the chest, shoulders, extremities and abdomen was a prominent feature in some patients with diaphragmatic tic.[1,11,15,17,18] In one patient the pain was severe enough to lead to an erroneous diagnosis of coronary thrombosis.[1] The chest distress was interpreted as referred pain resulting from disturbed function of the diaphragm. It was termed "cardiodiaphragmatic angina."[1] Some observers, however, who saw the same patient during later attacks commented on the fact that he manifested more theatrical behavior than was consistent with anginal attacks and that, in spite of his great distress, he was able to give an account of his heroic exploits as a deep sea diver.[2,4] It has been repeatedly demonstrated that faradic stimulation of an exposed phrenic nerve produced violent pain in the homolateral shoulder region.[17,20] One patient who suffered from tic of the right half of the diaphragm complained of marked pain in the right lower chest. Later in the course of the disease the pain was no longer felt although the tic of the diaphragm persisted.[18] In the majority of the cases reported in the literature, and in our own patients, pain was not a significant symptom. In one case in which tic of the diaphragm caused violent convulsions of the left side of the abdomen forceful enough to shake the bed the patient's general condition was described as "surprisingly unaffected."[16] Some patients with diaphragmatic tic complained of a feeling of "fluttering of the heart," or of "something going up and down like a clock all the time."[18] Exhaustion was the chief complaint in a group of patients who suffered from protracted attacks of diaphragmatic spasm. Some of these patients were still able to do their house work,[12,13] while in others the severe exhaustion and inability to do any manual work made surgical treatment imperative.[24]

Cyanosis was absent in the patients observed by us as well as in cases reported in the literature.[12,15,17]

Vibratory movements of the chest and abdominal wall observed on inspection and palpation were most helpful in the diagnosis of respiratory tic. In the presence of diaphragmatic spasm rapid vibrations were observed in the upper abdominal portions whence they extended toward the lower half of the chest. In some instances a throbbing sensation was felt on palpation of the lower thorax regions,[5] or a "flickering motion" was observed over the lower intercostal spaces.[2] Fluoroscopy revealed vibrations of the diaphragm in the absence of, or superimposed upon, normal respiratory excursions. In two instances of tic of the left half of the diaphragm which was synchronous with the heart beat a violent pulsation was observed in the left half of the abdomen.[16,25] When the right half of the diaphragm was involved, fluttering movements were occasionally seen just below the right costal arch.[18] In two patients who exhibited frequent and intermittent bouts of diaphragmatic spasm several rapid oscillatory movements of the abdomen,[19] or three to four "uncontrollable, jerky, abortive respiratory efforts,"[24] were described.

Tic of the intercostal muscles was manifested by a characteristic see-saw movement of the anterior thoracic wall.[7] The middle and upper portion of the chest were pulled in, while the lower, lateral areas of the chest bulged outward. In a few instances of diaphragmatic spasm and tic of the intercostal muscles rapid vibrations of the entire trunk were noted.[8,9,11]

Auscultatory Phenomena. Peculiar muscular sounds were heard in instances of intercostal as well as diaphragmatic tic. They were described by various authors as to-and-fro shuffle, sometimes resembling a pericardial friction rub, or as tick-tock, tapping, swishing or churning sounds. Their muscular origin was suggested by the fact that their rhythm differed from that of the heart beat and their point of maximum intensity was often outside of the precordial region. In the presence of diaphragmatic tic the sounds were loudest over the lower portions of the chest. In one instance in which the spasm involved only the right half of the diaphragm the muscular sounds were audible only over the right half of the chest.[18] The intensity of the muscle sounds varied greatly in the same patient as did the force of the vibratory movements.

Laboratory findings were rarely significant. In two patients[14–16] a shift of the blood pH toward the alkaline side occurred because of excessive loss of carbon dioxide through hyperventilation.

Mechanism and Etiology. Tic of the diaphragm may be caused by (1) a disturbance in the central nervous system; (2) stimulation of the phrenic nerve along its course; (3) a peripheral disturbance which stimulates either the terminations of the phrenic nerve or the diaphragmatic muscle directly.

Central stimulation of the phrenic nerve in the majority of the cases is a result of epidemic encephalitis.[12,15,17,20,22,24] Diaphragmatic tic is probably analogous to the tremor of paralysis agitans, and usually follows the encephalitis after a few weeks, in some instances only after years. Psychogenic tic is less frequently observed. It was probably present in our patients with diaphragmatic tic. Skillern[12] quotes from the Italian literature the case of a gardner who was able to accentuate or inhibit at will his attacks of diaphragmatic tic.

Irritation of the phrenic nerve along its course may occur in the presence of scar tissue, tumors or abscesses which affect the nerve.[19] In one instance spasm of the diaphragm was attributed to the irritating action of a cervical rib.[21] Of particular interest are two cases of tetany in which spastic contractions of the left half of the diaphragm occurred synchronously with the heart beat.[16,25] The tic was interpreted as due to electrical or mechanical stimulation of the phrenic nerve by the contracting heart. The stimuli caused by the heart beat were thought to be ineffective under normal conditions; however, when the threshold of nervous excitability was lowered in the presence of tetany, they were considered sufficient to produce contractions of the diaphragm. In the two reported cases the diaphragmatic spasm ceased after treatment of the tetany. Tic of the left leaf of the diaphragm, synchronous with the heart beat, was observed in experiments on dogs in which the excitability of the phrenic nerve was altered by exposure, anesthesia or the effect of drugs.[18] The tic subsided after section of the phrenic nerve.

Peripheral disturbances acting along the termination of the phrenic nerve or on the muscle itself include: hemorrhage into the diaphragm, abdominal adhesions,[11] fractured xiphoid process,[19] intestinal obstruction,[20] peritonitis or diaphragmatic pleurisy.[18] In a case reported by Harris and Scherf[18] flutter was confined to a portion of the right leaf of the diaphragm. It was not affected by block of the right phrenic nerve. When it ceased spontaneously, it could be readily produced by deep breathing. The authors believed that an altered metabolic state in a portion of the diaphragm might cause an abnormal response to physiologic stimuli. Thus the normal stimulus of breathing gave rise to a series of rapid spasmodic contractions of the diaphragm, just as in a heart with ischemic damage of the myocardium a single stimulus experimentally applied often produces an attack of paroxysmal tachycardia.

It is remarkable that in the two patients with diaphragmatic flutter observed by the authors mitral stenosis and marked enlargement of the heart were present. It is difficult to evaluate the significance of this factor in the genesis of respiratory tic.

As regards the see-saw movement of the anterior chest wall, Schreiber[7] thought that at least one component of this movement, namely, the protrusion of the lower lateral portions of the chest, was caused by rhythmic contractions of the external intercostal muscles. It is known that the function of these muscles is to raise the ribs during inspiration. Schreiber's view was

supported by the observation that the propulsatory movements ceased during forced inspiration when the intercostal muscles were refractory to extra stimuli. Schreiber thought that tic of the external intercostals was responsible for the hardening of the intercostal tissue and bulging of the ribs which caused the erroneous impression of a forceful apical thrust. On the other hand, the pulling in of the middle and upper portions of the thoracic wall was attributed by Schreiber to the effect of mediastino-pericardial adhesions, although the author was well aware of the objections to such an interpretation.

Holler[8,9] agreed with Schreiber as to the interpretation of the propulsatory movements but rejected the theory that pericardial adhesions were instrumental in the production of retractions of the chest wall. He believed that both components of the see-saw movement could be explained by the action of two antagonistic muscle groups. While the external intercostals have the effect of raising the ribs, the internal intercostals act as expiratory muscles, causing a depression of the thoracic wall. Because of the peculiar arrangement of these two muscle groups Holler felt that their simultaneous innervation had the effect of protrusion of the lateral and lower portions of the chest due to the contraction of the external intercostals, and depression of the middle thoracic portions due to the action of the internal intercostals. Thus, a see-saw movement of the thoracic wall was produced.

When a disposition to spasm is present any local stimulus such as the mechanical effect of the cardiac thrust against the chest wall or the electrical stimulus of the action potential of the heart might precipitate contractions of the irritable muscle group.[16] This would explain why at times the movements of the chest wall were synchronous with the heart action. At other times, when the rhythm of the contractions of the intercostal muscles deviated from the heart rhythm, it was probably controlled by nervous influences or possibly by a regulating mechanism inherent in the affected muscle, similar to the automatism of the myocardium.[8]

Organic neurologic abnormalities were absent in the cases of see-saw movement of the thoracic wall. All three patients of this group, however, showed psychopathic features. In our Case III the patient exhibited hysterical hyperventilation and was a morphine addict. The latter factor especially had a distinct influence on the manifestations of tic of the chest wall.

Precipitating Factors. According to Wechsler[26] tic is aggravated by emotions and ceases during sleep. Emotions, indeed, are frequently mentioned as an aggravating factor in both tic of the diaphragm[12,24] and intercostal muscles.[8,9] Other precipitating factors are deep breathing or cough,[18,24] sneezing[2] and exertion.[24] In one instance in which diaphragmatic spasm was attributed to the irritating effect of abdominal adhesions, attacks were regularly produced by intake of food.[11] Tic of the diaphragm was repeatedly observed to persist during sleep.[19,21,23,24]

Diagnosis. Some manifestations of respiratory tic such as "pulsations" of chest and abdomen, bruits heard over the chest in rapid and irregular sequence, and complaints of severe chest pain often gave rise to erroneous diagnoses. Adhesive pericardial disease and aneurysm of the aorta,[7] dissecting aneurysm,[16] auricular fibrillation[3] and coronary occlusion[1,4,5] were some of these. Such errors could be easily corrected on the basis of normal cardiovascular findings and discrepancies between the rhythm of the heart beat and that of the "pulsations" and sounds heard over the chest.

Once the movements of the chest and abdominal walls, and the auscultatory findings, have been recognized as independent of the heart beat, tic of respiratory muscles is the most likely diagnosis. When the vibrations are most marked in the upper abdominal region and the sounds are best heard over the lower parts of the chest, diaphragmatic spasm is probably present. The diagnosis is confirmed by fluoroscopic observation of rapid oscillations of the diaphragm. Fluoroscopy may at times reveal weak oscillations of the diaphragm, even when no vibrations are noticeable in the epigastric region.[16]

Tic of the intercostal muscles is characterized by the peculiar see-saw movement of the anterior thoracic wall. This movement has a much greater tendency than has diaphragmatic spasm to maintain the same rhythm as the heart beat for long periods of time. Eventually, however, an incongruity between the "pulsations" of the chest and the heart action becomes manifest. This finding and the absence of other cardiovascular abnormalities point to the presence of tic of the intercostal muscles.

Clinical Course. Tic of the respiratory muscles may last from a few seconds to several weeks or

months. It has a tendency to recur and to last longer and finally to become "almost continuous.[13] One case is reported in which bouts of diaphragmatic tic initially occurred daily at the same hour and lasted for a few seconds only. After several weeks the attacks recurred every hour and finally the spasm persisted day and night, incapacitating the patient from any kind of manual labor.[24] Porter[1] quoted a case reported by Simonin and Chavigny in which diaphragmatic tic had shown little tendency to improvement during twenty-seven months of clinical observation.

Treatment. In a few instances it is possible to attack the cause of tic. Treatment of tetany,[16,25] removal of a cervical rib[21] or of a fractured xiphoid process[19] were reported to have brought permanent relief from diaphragmatic spasm. On the other hand, administration of drugs such as dilaudid, luminal, inhalation of 10 per cent carbon dioxide or avertin anesthesia caused transient improvement at most. In one case of myogenic tic of the diaphragm, which persisted even after block of the phrenic nerve, quinidin seemed to have a favorable effect but did not give permanent relief.[18] Faradic stimulation of the phrenic nerve was beneficial in an occasional instance.

Prompt relief of diaphragmatic tic resulted as a rule from block of the phrenic nerves by procain[1,2] or freezing.[4,17] However, the effect of block was usually short, although in one patient after freezing of the phrenic nerve diaphragmatic tic did not recur for a period of seven months. Section or crushing of the phrenic nerves usually produced only transient relief.[2,11,13,17,20] Regeneration of the severed nerve fibers, as a rule, occurred within a period of nine months. Spasm of the diaphragm can be relieved permanently only by total avulsion of the phrenic nerves.[13] The inactivity of the diaphragm thus produced is usually remarkably well tolerated.[13,17,24]

Little is known about effective treatment of tic of the intercostal muscles. In our Case III, in which we were dealing with a morphine addict, the tic was aggravated by withdrawal of the narcotic and relieved by administration of morphine.

SUMMARY

Two cases presenting flutter-fibrillation of the diaphragm and one instance of tic of the intercostal muscles are reported. In addition, seventeen cases of tic of the respiratory muscles reported in the literature are reviewed. The total of twenty cases included seventeen instances of diaphragmatic tic and three cases of tic of the intercostal muscles. Singultus was not included in this study.

The clinical features, mechanism, etiology, diagnosis and treatment of the two types of respiratory tic are discussed.

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Interrelations between Hiccup and the Electrocardiogram*

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THE author has been impressed for a long time by the anatomical proximity between the phrenic nerves and the heart, and has harbored the suspicion that stimulation of these nerves by the electric currents produced during the heart beat might be responsible for some forms of hiccup and diaphragmatic tic. Since Carlo Matteuci as early as 1842[1] could produce contraction of one frog muscle by laying the nerve of this muscle across another contracting muscle, it seemed that similar conditions might exist in the case of the heart. Contraction of the diaphragm synchronous with the heart beat has been observed earlier[2–6] and could be postulated in some published cases of diaphragmatic tic.[7b] Accordingly, when the author encountered cases of postoperative hiccup in which each contraction of the diaphragm elicited a distinct artifact in the electrocardiogram, such as was described[5,6,8,9] and analyzed[10] earlier, he decided to make a detailed study of the relations between these artifacts and the electrocardiographic complexes.

METHOD OF STUDY

A Sanborn Poly-Viso direct-writing electrocardiograph with four channels was employed. In each case the standard limb leads and then the unipolar chest leads V_2, V_4 and V_6 were registered synchronously with the heart sounds, taken with a magnetic microphone with its membrane in direct contact with the chest wall. The sensitivity of this sound-recording system was 5–100 cycles per second. In all cases the moment of the hiccup was registered as a series of coarse vibrations, readily distinguished from the heart and breath sounds. Measurements were made from the earliest point of the QRS complex in any of the leads[11] to the beginning of these coarse vibrations. As the microphone was in direct contact with the chest there was no delay of sound conduction to be taken into consideration. If hiccup was accompanied by clearly visible artifacts in the electrocardiogram, the beginning of these artifacts was taken as the point of measurement rather than the beginning of the mechanical vibrations. Because of superposition on the vibrations produced by the heart beat, the latter point was sometimes difficult to determine with sufficient accuracy. The electrical artifacts usually began about 0.01 to 0.02 second before the mechanical vibrations. (Fig. 1.)

In some cases (Fig. 1) the respiratory movements produced a distinct wandering of the base line and the phases of respiration could be determined from this. In others it was necessary to observe the respiratory movements closely during registration and to press the signal or standardization button at the height of inspiration. The time interval in seconds between the last inspiration and the hiccup was measured on the tracing. If a hiccup occurred at the beginning of the tracing before the height of inspiration could be registered, the interval between the hiccup and the next moment of inspiration was measured and expressed as a negative number.

Although a large number of cases was studied, the moment of hiccup could be registered in a satisfactory way and a sufficient number of times only in five instances.† In four of these hiccup appeared for a brief period after abdominal operations, while one case suffered from arteriosclerotic heart disease. Serum electrolyte studies were performed in all of these,

† Dr. B. Surawicz registered the electrocardiograms in two of these cases, and the author wishes to express his thanks to him at this time.

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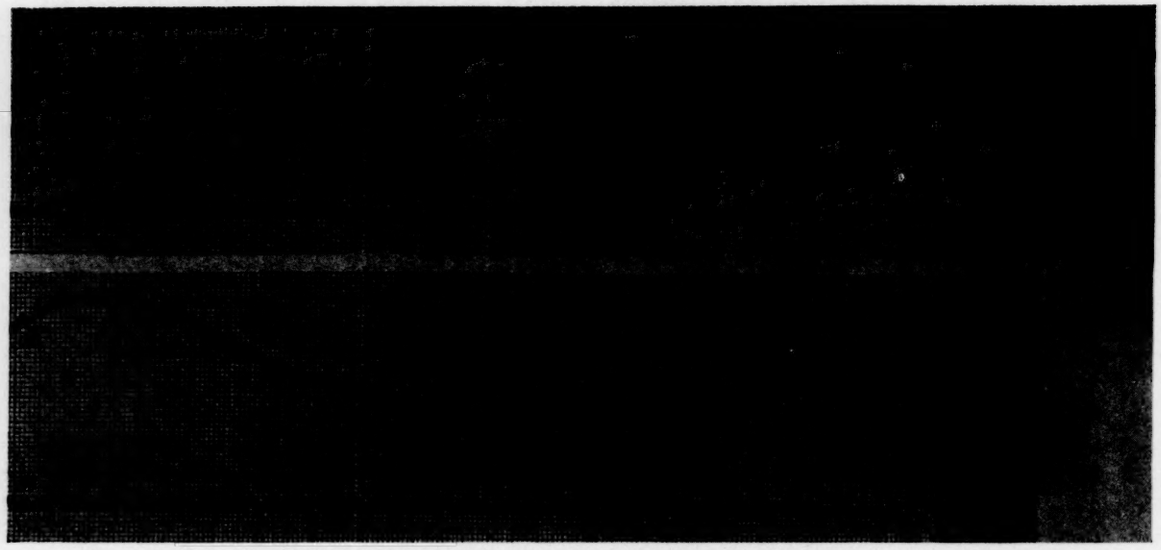

FIG. 1. Representative segment of the electrocardiogram of Case 4 during hiccup. The lower tracing is continuous with the upper tracing. Only lead II, registered synchronously with the heart sounds, is shown. The electrocardiographic artifacts due to hiccup are marked by arrows. At the end of the upper tracing there are two consecutive heart beats, each of which is followed by hiccup. The electrocardiogram shows variations of the base line synchronous with respiration, inspiration being accompanied by upward movement of the line.

and will be mentioned in the comments. The results were very similar in all five cases.

RESULTS

Of the five cases examined, two showed no electrocardiographic counterpart of the hiccup movements of the diaphragm. In one case (Fig. 1) sharp upright deflections appeared in leads II and III only, but not in any of the chest leads. These deflections could easily be mistaken for extra P waves and interpreted as auricular extrasystoles or "reciprocal beats" due to retrograde excitation of the auricles from the ventricles. Such a diagnostic error is especially apt to occur if the person interpreting the tracing is not aware of the presence of hiccup. However, in this case the presence of normal P waves immediately after the extra waves, at a time which would have corresponded to the auricular refractory period if the extra waves had really been of auricular origin, prevented such an error. It is possible that some of the bizarre extra waves at the end of the T wave reported previously without explanation[12] could have been due to similar artifacts caused by unrecognized hiccup. In the other case (Fig. 2) the hiccup artifact is of longer duration and can be confused with an irregularly appearing U wave. In this instance the artifact appeared only in leads V_{5-6} and to a slight degree also in V_4 but in no other leads.

The electrocardiographic artifacts due to hiccup cannot represent the action potentials of diaphragmatic muscle, as the contraction of this muscle is a tetanic one and would cause only high frequency vibrations similar to the somatic muscle tremor in the electrocardiogram. There is the possibility that the hiccup artifacts could be due to deformation potentials arising in the abdominal viscera. There are no observations which could prove or disprove this possibility but such deformation potentials could have only a very small influence on the electrocardiogram due to their small voltage and their location at a distance from the electrodes. On the contrary, deformation potentials of the skin, arising as a consequence of varying pressure of the electrodes caused by the hiccup movements, would cause major deflections in the electrocardiogram since they originate directly at the electrodes. Hiccup movements must invariably cause movements of the body as a whole in the elastic subcutaneous tissues, and such movements can very well lead to varying tension of the cables leading to the electrodes.[10] In the case in which the artifacts were present only in leads II–III the left leg electrode was probably the site of origin. In this case wandering of the base line synchronous with respiration was also present only in leads II–III. In the case in which the artifacts were present only in the left lateral precordial

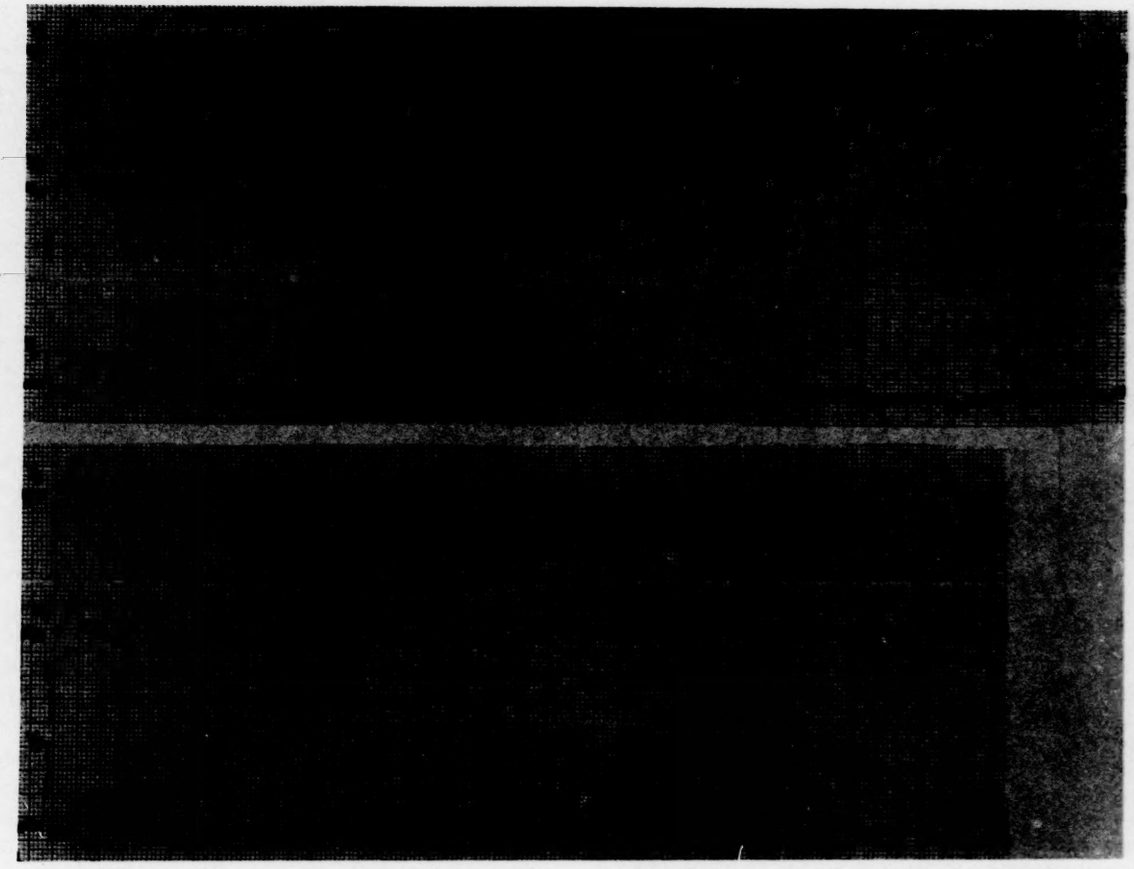

FIG. 2. Representative segment of the electrocardiogram during hiccup in Case 5. Only the leads V_2, V_4, and V_6, registered synchronously, are shown. The lower tracing is a direct continuation of the upper tracing.

leads these electrodes were apparently the only ones affected. In this case it could be clearly seen that the pulsations of the epigastric region associated with hiccup were confined to the left side.

In Case 2 of Table 1 the hiccup artifact caused a gross and readily recognizable displacement of the entire base line. (Fig. 5.) The unusual feature in this case was the sudden change in the QRS axis during this artifact, which could be mistaken for transient aberrant intraventricular conduction or ventricular fusion beats, if the presence of hiccup were not known to the person interpreting the electrocardiogram. These changes in the QRS axis are probably caused by sudden changes in the anatomical heart position during hiccup.

As can be seen from Table 1 and Figure 3, the hiccup movements in the five cases studied are not distributed at random throughout the cardiac cycle but appear only 0.17 to 0.40 second after the beginning of the QRS group. Usually every third to eighth heart beat was accompanied by a hiccup but on two occasions this appeared after two consecutive heart beats. (Case 4, Fig. 1; Case 5, Fig. 5.) This proved definitely that the heart beat was the cause of the hiccup in the cases under consideration although the exact mechanism of this relation still remained unsettled. Especially perplexing was the wide range of variability of the interval between QRS and the hiccup in the same person. It was thought that correlation of this interval to the phase of respiration during which hiccup occurs might reduce this range, and this supposition proved to be correct.

Figure 3 represents the relation of the interval from the beginning of QRS to the beginning of the hiccup artifact movement in 65 hiccups of Case 4. It can be seen that this interval ranges from 0.24 to 0.36 second at the height of inspiration and immediately preceding it, and from 0.18 to 0.30 second during the expiratory phase. At the same time it is clear that the hic-

cups are scattered evenly through all phases of respiration.

COMMENT

In order to understand the mechanism by means of which the heart beat can elicit a hiccup, it is necessary to visualize the anatomical relations between the heart and the phrenic nerves. As can be seen from Figure 4, both phrenic nerves are imbedded in the anterior section of the pericardium and are thus in intimate contact with the heart for a distance of 10 to 15 cm. The right phrenic nerve is in contact only with the right auricle, while the left phrenic nerve is in contact with the left ventricle and also with the left auricular appendage. The possibility exists, accordingly, that the scatter in the time of appearance of the hiccup in relation to each heart beat might be due to excitation of the phrenic nerves, sometimes by the auricular action potential (P wave) and sometimes by the ventricular QRS group. However, if this actually were so two distinct groups of intervals would have been apparent, and this was not the case. The maximal voltage of electrocardiographic waves which can be registered from the surface of the auricles is about 20 millivolts while that registered from the ventricular surface exceeds 50 millivolts.[13] It must therefore be assumed that whenever the excitability of the phrenic nerves increases, these nerves are stimulated first by the ventricular complex and, if there is extreme hyperirritability, by the auricular complex which precedes the ventricular complex.

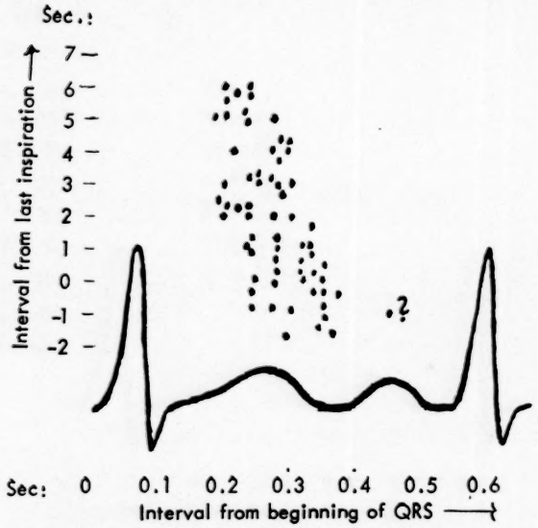

FIG. 3. Chart showing correlation of the interval from the beginning of QRS to the beginning of the hiccup artifact with the interval from the peak of the last inspiration to this artifact in Case 4. The electrocardiogram in lead V_4 has been drawn on the same coordinate system to demonstrate the time of appearance of the intrinsicoid deflection. The single point accompanied by a question mark is the only hiccup artifact to appear more than 0.40 second after beginning of QRS; it probably represents a spontaneous hiccup unrelated to the heart beat.

TABLE I

Case	Diagnosis	No. of Hiccups Registered	Interval from Beginning of QRS (sec.)	Q-T_c (%)
1	Post-cholecystectomy	5	0.23–0.30	+22
2	Gastric ulcer	10	0.28–0.40	+15
3	Post-appendectomy	6	0.22–0.30	+16
4	Intestinal obstruction	65	0.20–0.38	+18
5	Arteriosclerotic heart disease	13	0.17–0.39	+20

The most rapid change of potential on the cardiac surface occurs in the form of the so-called "intrinsic deflection" when the excitation reaches the ventricular surface. In the region where the left phrenic nerve is in contact with the left ventricle, this deflection occurs about 0.05 second after the beginning of the QRS complex.[10] The latent period between actual excitation of the nerve and the response in the form of the hiccup is accordingly 0.5 second less than the value given in Table I, or 0.12 to 0.34 second. As the speed of conduction in the motor neurons of the phrenic nerves is of the order of 50 to 100 meters per second,[14] only about 0.01 second of this interval could be accounted for by conduction along the phrenic nerve to the diaphragm, and another 0.01 second by the delay of transmission in the myoneural junction. This leaves the greater part of the latent period of the hiccup unaccounted for.

The nature of the latent period can be explained best if it is kept in mind that it is not the contraction of the diaphragm itself but its repercussions on the larynx or the electrodes which were brought in correlation with the electrocardiogram. The peculiar sound of hiccup appears only when the negative pressure in the chest cavity caused by the sudden diaphragmatic contraction becomes intense enough to cause

sudden closure of the vocal chords. Similarly, the electrocardiographic artifact appears only when the movement of the body has progressed far enough to cause stretching of the electrode cables. From this point of view the great variability of the latent period becomes entirely comprehensible.

The factors discussed in the preceding paragraph also explain the dependence of the latent period on the phase of respiration. The latent period for the isometric contraction of frog skeletal muscle was from two to ten times as short when the muscle was stretched than when it was half this length.[15] The interval in which a certain tension was attained was up to 0.3 second shorter in the former than in the latter case. When the diaphragm is in the inspiratory position, the muscle fibers which are still quiescent at this time and which are excited by stimulation of the phrenic nerve will cause an appreciable movement of the diaphragm only when they become shorter than the surrounding contracted muscles. In contrast to this, when stretched in the expiratory position they will produce movement of the diaphragm almost immediately. On the other hand, it will take a greater movement of the diaphragm to produce the same change in intrathoracic pressure when the lungs are expanded than when they are collapsed in expiration, and it will correspondingly take longer for the hiccup sound to appear in the former than in the latter case.

In addition to the mechanism just discussed, part of the delay between the QRS complex of the electrocardiogram which stimulates the phrenic nerve and the response in the form of the hiccup could be explained by assuming that not the motor but the sensory fibers of the nerve are stimulated, and that the contraction of the diaphragm takes place by way of a reflex arc passing through the central nervous system. This assumption can be proved or disproved only by registering the action potentials of the phrenic nerve. It does not seem very likely.

An important question is what causes the phrenic nerve to become excitable by the cardiac action potentials. One of the most important factors responsible for this seems to be a decreased concentration of ionized calcium, which decreases the accommodation and thus increases the irritability of nerve.[14,16] In all previously reported cases of diaphragmatic contraction synchronous with the heart beat, hypocalcemia was present[2–6] or there was alkalosis.[7a,7b] Hypocalcemia was also held responsible for many cases of postoperative hiccup.[17] In the present series, which included four cases of postoperative hiccup, the serum calcium was normal but Chvostek's sign was present in two cases. Furthermore, the corrected Q-T duration was prolonged beyond 20 per cent in all cases; this is suggestive, while not indicative, of a decrease in the ionized calcium.[10,18] It is interesting that in Case 4 the hiccup as well as Chvostek's sign appeared when the hypopotassemia present immediately after operation was corrected by infusion of potassium and the serum potassium rose from 3.2 to 3.9 mEq./L. This is in analogy with previous observations[19] according to which the manifestations of tetany in sprue may appear only when the concomitant hypopotassemia is corrected. The question might be asked why hiccup is not present in all cases of tetany. One possibility is that in pronounced cases diaphragmatic contractions synchronous with the heart beat might be present, as in the cases referred to in the introduction, and these can remain unobserved or at least not be considered

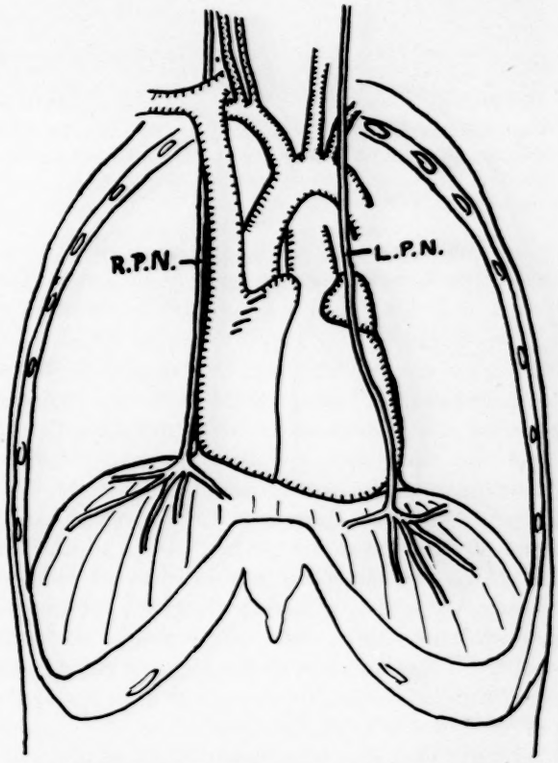

FIG. 4. Sketch representing the relation of the right phrenic nerve (R.P.N.) and the left phrenic nerve (L.P.N.) to the heart.

FIG. 5. Electrocardiographic artifacts due to hiccups in Case 2, synchronously registered leads I to III and heart sounds. In the first half of the tracing a single hiccup is visible, while the second half contains a double hiccup elicited by two successive heart beats.

as hiccup. Another, more likely possibility is that other factors must be present in order that tetany may lead to diaphragmatic excitation.

The question still remains as to what percentage of the hiccup cases owe their symptoms to stimulation of the phrenic nerve by cardiac activity. This mechanism was undoubtedly at work in the cases of diaphragmatic flutter mentioned in the introduction and in the five cases presented in this paper. On the other hand, cases of diaphragmatic tic have been published in which synchronous registration of hiccup sounds with the electrocardiogram definitely showed that both were independent of each other.[22,23] Registration of the electrocardiogram synchronously with the sounds in a larger number of cases is urgently needed to clarify this problem. This can be accomplished easily with any conventional electrocardiograph by registering one of the leads through an electromagnetic radio head-phone whose membrane is in contact with the chest. The hiccup sound will then be superimposed on the electrocardiographic curve, readily allowing the study of the mutual time relations.

While the causation of hiccup by the electric currents produced by the heart is of considerable theoretical interest, it also has some practical implications. In cases of intractable hiccup, in which this abnormality may be extremely exhausting and even lead to death, the practical suggestion to be inferred as far as treatment is concerned would be to try insufflation of the pericardium with air. Even a small amount of an electrically non-conducting gas or liquid would be sufficient to prevent the electric currents generated by the heart from reaching the phrenic nerves. The beneficial effects of treatment with calcium salts, parathyroid hormone and dihydrotachysterol on hiccup would be obtained regardless of whether it is caused by the electric currents produced by the heart or by central or reflex excitation of the phrenic nerves.

SUMMARY

1. In five cases of recurrent hiccup the hiccup sounds were recorded synchronously with three leads of the electrocardiogram.

2. In three cases the hiccup movements caused electrocardiographic artifacts which could be confused with U waves or with auricular and ventricular premature beats.

3. The hiccup sounds as well as the artifacts always occurred 0.17 to 0.40 seconds after the beginning of the QRS complex of the electrocardiogram, and in some cases two successive heart beats were followed by hiccup movements. It is postulated that in the reported cases the hiccup was caused by stimulation of one of the phrenic nerves by the electric currents registering as the QRS complex of the electrocardiogram.

4. The hyperirritability of the phrenic nerves in the reported cases was probably due to a decrease in the ionized serum calcium or to alkalosis.

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Review

The Mechanics of Pulmonary Ventilation in Normal Subjects and in Patients with Emphysema*

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THE chief symptom in pulmonary emphysema is difficulty in breathing. Study of patients with this disease reveals inability to achieve a high rate of air flow during expiration and a marked limitation in the maximum breathing capacity.[1,2] Thus there is reason to believe that an increased force is required to move air in and out of the lungs.

Studies of intrapleural pressure in patients with pulmonary emphysema have shown large fluctuations in pressure during quiet breathing, suggesting that an increased force is required to ventilate the lungs.[3–6] These studies have been limited because of the dangers in inducing pneumothorax in patients with emphysema. The demonstration that intraesophageal pressure is an acute measure of changes in intrathoracic pressure permits a much more detailed study of the mechanics of ventilation in this disease.[7] In a previous study the elastic, or static, forces of the lung were measured.[8] The purpose of the present study is to examine the kinetic forces involved in ventilation of the lungs.

REVIEW OF THE MECHANICS OF VENTILATION

The intrathoracic pressure may be looked upon as the algebraic sum of a number of different pressures. These pressure components may be divided into three general categories. The first is the pressure used to accelerate the system; that is to say, the heart, blood, lung parenchyma and its contained gas. This has been shown on theoretic grounds to be negligible when compared to the other pressure components.[9]

The second general pressure component is that portion of the intrathoracic pressure used to overcome the retractive force, or elastic properties, of the lung. This pressure bears a close functional relationship to the amount of lung distention, much as the force on the ends of a rubber band is related to the amount of stretch. This represents the potential energy of the system, since the work done on the elastic system during inspiration is returned during expiration except for a minor increment lost due to hysteresis. This pressure component representing the elastic forces of the lung has been shown to contribute significantly to the intrathoracic pressure.

The third component of the intrathoracic pressure is that required to overcome the frictional resistance of the lung and contents. This pressure is a function of movement of the lung, unlike the elastic pressure. This pressure is composed of only two significant components. These are: (1) the pressure required to overcome the viscance, or frictional resistance to movement of the lung parenchyma and other tissues of the intrathoracic cavity, and (2) the pressure required to overcome resistance to gas flow along the bronchial tree.

A general equation for intrathoracic pressure

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relating these various components may be written:

$$P_T = P_L + P_V + P_P \quad \text{(Equation 1)}$$

P_T is the intrathoracic pressure; P_L* is the pressure caused by the retractive force of the lung; P_V is the pressure required to overcome tissue friction; P_P is the pressure difference between the alveoli and the oral cavity which is required to produce gas flow along the bronchial tree. The pressure term for the acceleration is ignored. Note that these pressures are related to the atmosphere and consequently P_L will be negative under normal circumstances; P_V and P_P will be negative on inspiration and positive on expiration. Consequently, P_T may become positive on expiration if the values for P_V and P_P are large. Since P_V and P_P are functions of movement of the lung, they will be zero under static conditions.

The pressure P_V, which is a measure of the frictional forces opposing deformation of the tissue during expansion or retraction of the lung, is independent of the type of gas breathed. It is a quantity which is not directly measured although, as will be shown, it may be calculated. The resistance to gas flow through the various channels of the respiratory tree, which is measured by P_P, will be a function of the rate of flow, of the density and viscosity of the inspired gas, and of the dimensions of the system through which it is flowing.

In considering gas flow resistance three types of flow may be distinguished: laminar, turbulent and eddying turbulence.[10] Laminar flow is characterized by a completely orderly behavior of the gas so that the particles follow a line parallel to the axis of flow and do not deviate from this path. Turbulent flow, on the other hand, is characterized by extremely chaotic motion of the gas particles so that they follow a violently irregular course. The third type of flow may be thought of as localized turbulence or eddy formation. This occurs as the stream passes through sudden enlargements or constrictions of the flow channel and with changes in direction of the stream.

Rohrer[9] first suggested that only two of the types of flow, laminar and eddying turbulence (Extrawiderstand), are of importance in the respiratory tree at flow levels less than cough or sneeze.* Laminar flow occurs along the smooth, straight channels of the respiratory tree. Eddying turbulence occurs at points where the gas flow changes direction or velocity, such as at bifurcations, bends and sudden enlargements or constrictions of the respiratory passages.

Where laminar flow exists, the pressure drop required to overcome the frictional resistance is directly proportional to the rate of flow, to the viscosity of the gas and to the length of the tube. On the other hand, the pressure drop required is inversely proportional to the fourth power of the diameter of the tube. Thus if flow, viscosity or tube length is doubled, the pressure drop required is doubled; but if the diameter is halved, the pressure drop required is increased sixteenfold. One may alter the density of the gas with no change in the pressure drop required to produce a given gas flow. These factors are mathematically related in Poiseuille's law.

Where eddying turbulence exists, the pressure drop is proportional to the density of the gas and to the square of the flow. Thus if the density is doubled, the pressure drop required to maintain a given level of flow is doubled. On the other hand, it is necessary to increase the pressure drop fourfold to double the flow. The pressure is independent of viscosity in turbulent flow.† In an extremely detailed study Rohrer[9] applied these physical principles to air flow in the respiratory passages of man. By measurement of the diameter and nature of branching of the respiratory passages in cadavers and with several important simplifying assumptions, he calculated the resistance to air flow in the human respiratory tree. On the basis of these measurements, assumptions and calculations he derived a formula from which the pressure drop, P, from mouth to alveolus for a given flow, Q, of air in the normal respiratory tree may be calculated:

$$P = 0.79Q + 0.801Q^2 \quad \text{(Equation 2)}$$

P is in centimeters of water and Q is in liters per second. The first term, which is directly proportional to flow, represents the part of the pressure required for laminar flow. The second term,

* P_L is a negative pressure when measured by the intrathoracic pressure. In the previous paper it was used in the conventional sense as a positive quantity.

* Rohrer stated in his paper that the critical Reynolds number is not exceeded in the trachea at physiologic flow levels. Examination of his calculations reveals a tenfold error. Thus, contrary to Rohrer's statement, the critical Reynolds number is exceeded even during ordinary breathing.

† Strictly speaking, viscosity does have some small effect which may, however, be ignored for the purposes of this study.

which is proportional to the square of the flow, represents the portion of pressure required for turbulent flow. This formula assumes a rigid respiratory tree, a constant relationship between the amount of laminar flow and turbulent flow at all levels of flow, and equal ventilation to all parts of the lung. None of these is strictly true, as will be shown. For a more technical discussion of the physics of gas flow the reader is referred to any standard textbook.[10]

METHOD

Theory. In the study of the mechanics of ventilation it is essential to differentiate that portion of intrathoracic pressure which is related to the elastic forces of the lung and that portion which is related to frictional resistance to motion. Referring to equation 1, it will be noted that at zero flow $P_T = P_L$; that is, the intrathoracic pressure equals the pressure produced by the elastic force of the lung. P_L varies with the degree of inflation of the lung. Equation 1 can be rearranged as follows:

$$P_V + P_P = P_T - P_L \quad \text{(Equation 3)}$$

Thus the difference between P_T and P_L equals the force required to overcome tissue friction and gas flow resistance.

It is apparent from these considerations that measurements of intrathoracic pressure must be made both during motion of the lung and at zero flow. In a previous study intraesophageal pressure was shown to be an accurate method for measuring changes in intrathoracic pressure.[7] It also was shown that the retractive force of the lung (P_L) could be measured by stopping air flow through the mouth with a valve and measuring the differential pressure between the oral cavity and the esophagus.[8] In the present study the same principle was employed. The respiratory air flow was suddenly stopped with a rapidly acting valve while the subject was breathing. The differential pressure between the oral cavity and the esophagus immediately before closure of the valve represented $P_L + P_V + P_P$. The differential pressure after closure of the valve represented P_L. Assuming that the volume of the lung did not change during closure of the valve, the difference between these two pressures represented $P_V + P_P$. A pneumotachygraph tracing was recorded simultaneously. Thus $P_V + P_P$ could be related to the rate of air flow. By taking measurements at various rates of air flow a pressure-flow diagram was constructed.

To differentiate these two components of frictional resistance it was necessary to have the subjects breathe two gases with different physical properties. A pressure-flow diagram was constructed for each gas and these were compared. The difference in the pressure-flow relationship must be attributable to the different physical properties of the two gases breathed, since the tissue friction is independent of the gas breathed. The gas mixtures used were 80 per cent argon with 20 per cent oxygen, and air. The viscosity of argon-oxygen is 229 micropoise at 37°C. as compared with a value of 193.7 for air. The specific gravity of argon-oxygen is 1.33 as compared with 1.00 for air. Thus the resistance caused by both laminar and turbulent flow is increased as compared with air. Moreover, the ratio of laminar to turbulent flow remains approximately the same as air at varying flow levels. This permits the mathematical estimation of the resistance to gas flow as compared with that due to the frictional resistance of the lung tissue.

Procedure. Thirteen normal men, five normal women and fourteen men with pulmonary emphysema were studied. The diagnosis of pulmonary emphysema was based on the typical clinical findings, an increase in the ratio of residual air to total lung volume and a high value for nitrogen in the alveolar air after seven minutes of breathing oxygen.[13]

The intrathoracic pressure was measured through a special type of intraesophageal pressure recording balloon previously shown to record accurately changes in intrathoracic pressure.[7] The balloon was filled with approximately 2 cc. of helium and was thus in an almost completely collapsed state. It was necessary to verify the amount of gas in the balloon from time to time during the experiment. If a leak is present in the pressure recording system, the balloon will become distended with gas because of the negative intraesophageal pressure. The tube leading from the balloon (Fig. 1K) was attached to the positive side of a 2-pound per square inch differential strain gauge. (Fig. 1L.) The pressure just outside of the mouth (Fig. 1M) was transmitted to the negative side of the strain gauge. The output of the gauge represented the changes in intrathoracic pressure with respect to a point just outside the oral cavity. The subject breathed into a conventional recording spirometer circuit. A pneumotachygraph similar to the one described by Lilly[11] was introduced into

one arm of the circuit (Fig. 1A) for continuous recording of respiratory flow. A solenoid valve (Fig. 1B) was used for instantaneous electrical interruption of the respiratory flow. The system was first filled with air. The metabolic rate of the subject was computed and a steady flow of oxygen was carefully adjusted through an accurate displacement meter (Fig. 1C) to equal the subject's oxygen consumption as closely as possible. Thus a horizontal respiratory tracing (Fig. 1D) was obtained on the recording spirometer instead of the conventional sloping one. In this way a constant relationship was maintained between the position of the spirometer bell and the volume of the lung. In addition, the composition of the respired gas remained constant.

A plastic cam (Fig. 1E) was placed on the pulley of the spirometer so that a set of electrical contact points could be closed at any desired position of the cam. The points (Fig. 1F) completed an electrical circuit which produced instantaneous closure of the solenoid valve. By adjusting the position of the cam the respiratory flow could be interrupted at any predetermined position of the chest.

A simultaneous recording of respiratory flow and of intraesophageal pressure with respect to atmospheric pressure was obtained as the subject breathed. (Fig. 2.) When the respiratory flow was suddenly interrupted by the valve, a plateau appeared on the tracing which represented the elastic force of the lung. Since the valve closed rapidly, sharp shoulders were produced in both the recording of respiratory flow and the recording of the intraesophageal pressure. The distance from the plateau to a point immediately preceding closure of the valve in the intraesophageal pressure tracing (from *a* to *b* in Figure 2) represented the frictional portion of the intrathoracic pressure at the instant of closure of the valve. This pressure is

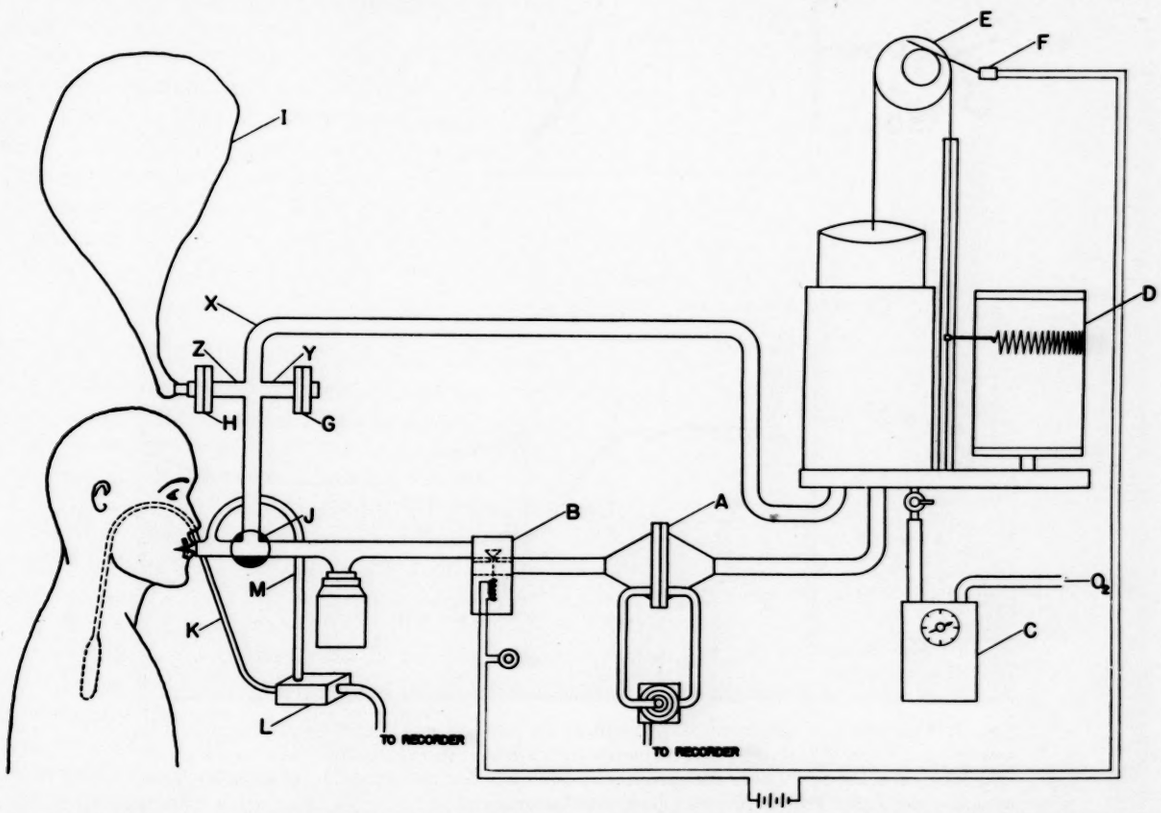


FIG. 1. Apparatus used in experiment; A, pneumotachygraph; B, solenoid interruptor valve; C, gas meter; D, recording spirometer; E, recording spirometer pulley with plastic cam; F, electric contact points; G, one-way exhaust valve; H, one-way intake valve; I, large plastic gas bag; J, three-way respiratory valve; K, tube connecting with intraesophageal balloon; L, 2 pound per square inch differential strain gauge; M, tap for intraoral pressure; X, position of clamp during equilibration of subject with gas; Y and Z, position of clamps during experiment.

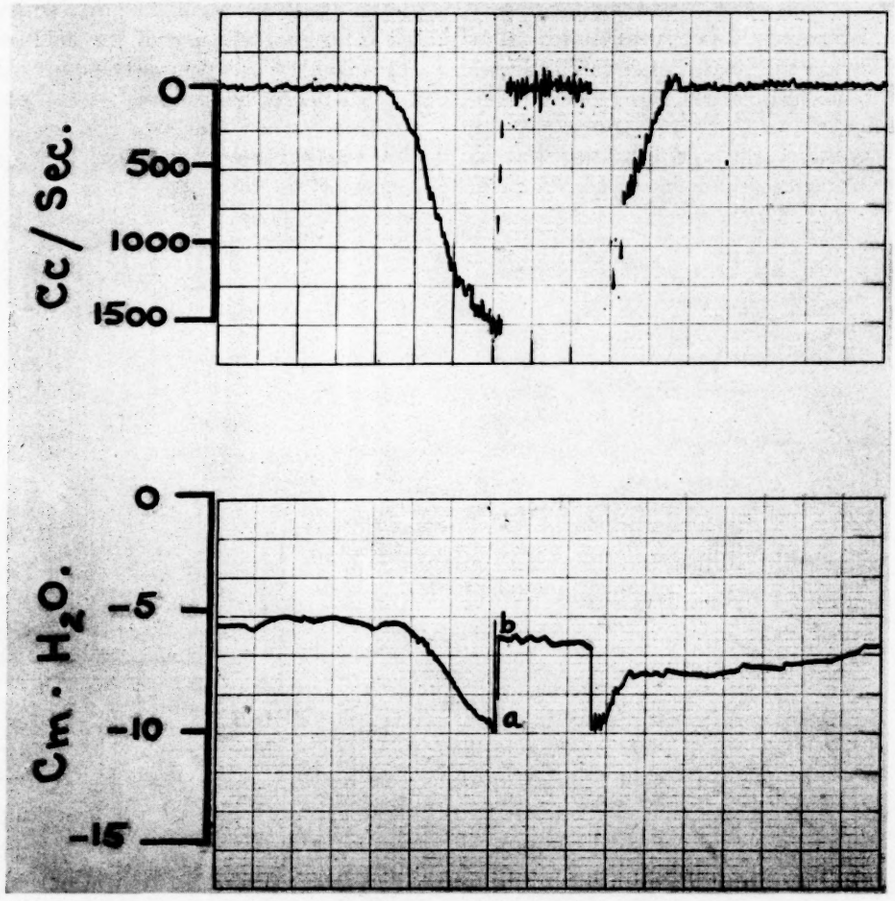


FIG. 2. The effect of interruption of respiratory flow on intraesophageal pressure. The upper tracing on this recording represents the rate of inspiratory flow in cc. per second. The lower tracing represents the simultaneously recorded intraesophageal pressure in cc. of water pressure. The respiratory flow was interrupted at (*a*).

composed of the sum of P_V and P_P in equation 1. The rate of respiratory flow was obtained from the pneumotachygraph tracing at the instant of closure. Varying rates of flow were obtained through the cooperation of the subject. Since the flow was interrupted each time at the functional residual volume, the extraneous variable of bronchiolar diameter due to differences in lung inflation was eliminated. From these measurements a pressure-flow curve was constructed. (Fig. 3.)

Multiple pressure measurements were made at each level of flow. There was often considerable variation in the individual measurements, particularly at high flow levels. For this reason the pressure-flow curves were constructed by taking the mean of a large number of measurements. In patients with severe emphysema the plateau in the intraesophageal pressure tracing was not formed immediately upon closure of the valve. Rather, a rounded slope preceded the plateau. This was attributed to a delay in the equilibration of the pressure in the various portions of the lung with the trachea. This emphasizes the importance of obtaining a truly static pressure measurement in evaluating the elastic forces of the lung and resistance to air flow in patients with emphysema.

To study the effect of argon-oxygen on the resistance to gas flow it was necessary to fill the spirometer circuit and to equilibrate the lungs of the subject with the gas mixture. First, the gas mixture was introduced into the spirometer circuit through a one-way valve (Fig. 1H) from a large plastic balloon. Then the subject was equilibrated with the gas mixture in the bag for seven minutes, using the open circuit method. The experiment was then begun. Because air

and argon-oxygen have different viscosities, the pneumotachygraph was calibrated with each gas before and after each experiment. It was also necessary to calibrate both inspiration and expiration. The pneumotachygraph was calibrated by comparing the integrated time-flow curve with the corresponding volume obtained from the spirometer tracing.

Three normal and four emphysematous subjects were studied at three different levels of lung inflation. Measurements were made 1 L. above, 1 L. below, and at the functional residual volume during inspiration and during expiration. This was accomplished by setting the cam so that the solenoid valve interrupted the flow when the chest came to the designated position.

RESULTS

Normal Subjects. The pressure-flow relationships in the normal subjects may best be seen by referring to the pressure-flow curves in Figure 3. Fig. 3A shows the relationship of inspiration to expiration in the normal subject breathing air. For a given flow it requires slightly more pressure during expiration than during inspiration.

The pressure-flow relationship between argon-oxygen as compared with air during inspiration in normal subjects may be seen in Fig. 3C. The argon-oxygen pressure-flow curve falls to the right of the air curve. Argon-oxygen and air have roughly the same tendency toward developing turbulence and, consequently, each will demonstrate approximately the same relative amount of laminar and turbulent flow at any given level of flow. Because both viscosity and density are increased, more pressure is required to produce a given flow when the subject breathes argon-oxygen than when he breathes air.

The pressure-flow relationship using air at three different chest positions may be seen in Figure 4 for inspiration and Figure 5 for expiration. The chest position has relatively little effect on the pressure-flow curve during inspiration. During expiration it is apparent that below the functional residual volume the pressure-flow curve bends more rapidly, indicating that as the volume of the lungs decreases the resistance to gas flow becomes progressively greater.

Emphysematous Subjects. Studies identical with those just described were performed on subjects with pulmonary emphysema. The striking finding was that much greater pressure was required to produce a given rate of gas flow in patients with emphysema than in normal subjects. (Fig. 3.) This was true both during inspiration and expiration. The expiratory pressure-flow curve in emphysema is of particular interest. (Fig. 3B.) With increasing flow the curve bends more and more until a point is reached at which further increase in pressure produces almost no further increase in flow.

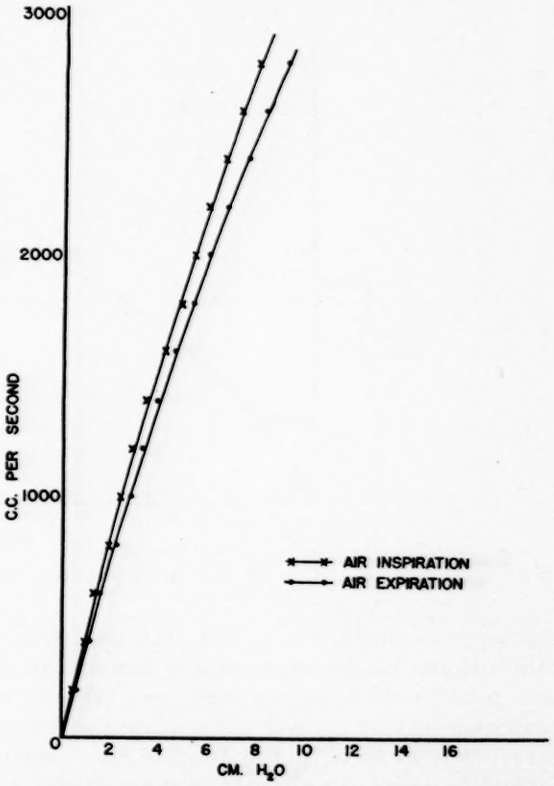


FIG. 3A. Pressure-flow curves (3A to 3D) in normal subjects and in patients with pulmonary emphysema. A, comparison of a mean inspiratory pressure-flow curve with expiratory curve of normal subjects breathing air.

The pressure-flow curves obtained from the patients with emphysema breathing air and argon-oxygen are shown in Figure 3D. The argon-oxygen pressure-flow curve lies to the right of the air curve. The marked difference between these curves indicates that the increased resistance to movement of the lungs in emphysema is caused by increased resistance to gas flow. This will be discussed in detail later.

The relationship of the pressure-flow curves to the position of the chest in emphysema may be seen in Figures 6 and 7. Notice that the inspiratory pressure-flow curves (Fig. 6) are only

moderately affected by chest position. On the other hand, the expiratory pressure-flow curves (Fig. 7) are very significantly altered. As the lung assumes positions of less and less inflation, the pressure-flow curves bend more and more and approach an asymptote at progressively lower levels of flow.

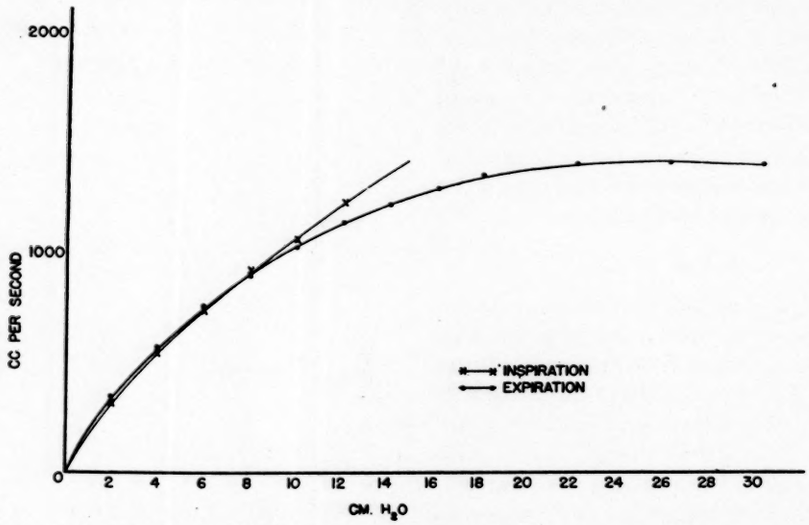


FIG. 3B. Pressure flow curves in patients with pulmonary emphysema.

Mathematical Analysis of Data. In the presentation of the results an empirical description of the pressure-flow curves has been given. A mathematical analysis of these curves is necessary if any form of quantitation of the various factors involved in resistance to lung movement is to be achieved. In particular, it is important to evaluate the resistance attributable to laminar gas flow, turbulent gas flow and tissue friction in normal subjects and in patients with pulmonary emphysema.

A finite series of expressions consisting of increasing powers of some variable is called a polynomial. If this polynomial can be used to represent the value of functionally related quantities, the coefficients of each term in the polynomial may be obtained by methods of calculus. Successive differentiation of such a function will yield the coefficients of the successive terms in the series.

Reasoning on purely physical grounds, at least part of the pressure-flow relationship in pulmonary ventilation must be expressible by such a polynomial. The first non-zero term of such a polynomial is the linear term, K_1Q. The second is the quadratic term, K_2Q^2. These two terms may be considered as the first two terms in a polynomial, of possibly higher degree.

A mathematical equation to describe the pressure-flow relationships in the respiratory tree must have physical as well as mathematical interpretation if it is to be meaningful as well as useful. An expression to describe the resistance to ventilation of the respiratory tree must have terms to represent the pressure increments required to overcome resistance to laminar gas flow, turbulent gas flow and tissue friction. The sum of these pressure increments is represented by ΔP which equals $P_T - P_L$ or $P_P + P_V$. (See equation 3). Since $P_P = [k_1\mu Q + k_2\rho Q^2]$ and $P_V = [f^{(Q)}_{tissue}]$ where Q is flow, μ is viscosity and ρ is density, then the total pressure drop, ΔP, may be expressed symbolically as:

$$\Delta P = [k_1\mu Q + k_2\rho Q^2] + [f^{(Q)}_{tissue}] \quad \text{(Equation 4)}$$

The linear term, $k_1\mu Q$, represents the laminar flow portion of the gas flow resistance, the $k_2\rho Q^2$ term, the turbulent flow resistance. The functional notation, $f^{(Q)}_{tissue}$, represents the tissue friction term. The nature of this tissue friction term is totally unknown. As will be shown experimentally, it is a negligible quantity. The laminar flow or linear term, $k_1\mu Q$, is derived from Poiseuille's Law. The k_1 part of the coefficient embodies the constants and the dimensions of the flow channels. μ is the viscosity. As will be shown, the dimensions are related to the intra-

thoracic pressure, P_T. Thus $k_1 = f(P_T)$.* No simple mathematical expression exists for this function.

The term, $k_2\rho Q^2$, represents the pressure drop to overcome the resistance of turbulent gas flow. The k_2 part of the coefficient embodies the constants and the dimensions of the respiratory tree. The density is ρ. As mentioned heretofore, the dimensions of the bronchiolar system are a function of the intrathoracic pressure, P_T. In addition, the dimensions of the upper respiratory tree, such as the glottis, may be related to the rate of flow, Q. Furthermore, with increasing rates of flow the Reynolds number increases. As a result the actual number of turbulent sites will increase with the increasing flow. Thus k_2 is a function of both flow, Q, and intrathoracic pressure, P_T.

Therefore, since k_1 equals f (P_T) and k_2 equals $f(Q,P_T)$, equation 4 should be rewritten:

$$\Delta P = [f(P_T)\mu Q + f(Q,P_T)\rho Q^2] + [f^{(Q)}_{tissue}] \quad \text{(Equation 5)}$$

As one approaches zero flow, the variable quantities $f(P_T)$ and $f(Q,P_T)$ become the constants k_1 and k_2, respectively, of equation 4. This is true since the amount of lung inflation was maintained constant; and therefore as zero flow is approached, the value of $f(P_T)$ will be a constant regardless of the gas breathed. Thus, one may consider equation 5 to be the simple polynomial equation 4 in the limit of zero flow.

To obtain the values of the complete coefficients of the linear and quadratic terms from the experimental curves, the first and second derivatives were taken. (Fig. 8.) This was done by measuring the tangent lines to the curves at successive levels of flow and then plotting these values against the flow. (Fig. 8B.) This represents the first differentiation. The intercept with the zero flow ordinate represents the value of the coefficient of the linear term. Successive tangents are then taken from this new curve

* The dimensions are not a simple function of the intrathoracic pressure but are related to the difference between the intrathoracic pressure and the pressure within the bronchiole at that point. It follows that the dimensions of the respiratory tree must therefore also be related to the flow. Furthermore, strictly speaking, the laminar flow term coefficient bears still another functional relationship to flow. That is, as the flow increases, the turbulent flow regime spreads at the expense of the laminar flow regime. This factor is probably minor compared to the others.

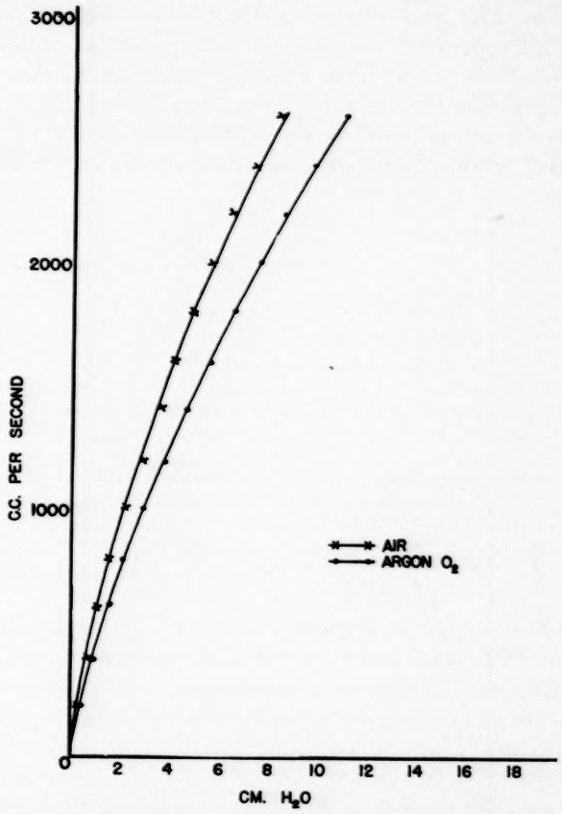


FIG. 3C. Comparison of a mean inspiratory pressure-flow curve of normal subjects breathing air with the curve of subjects breathing argon-oxygen mixture.

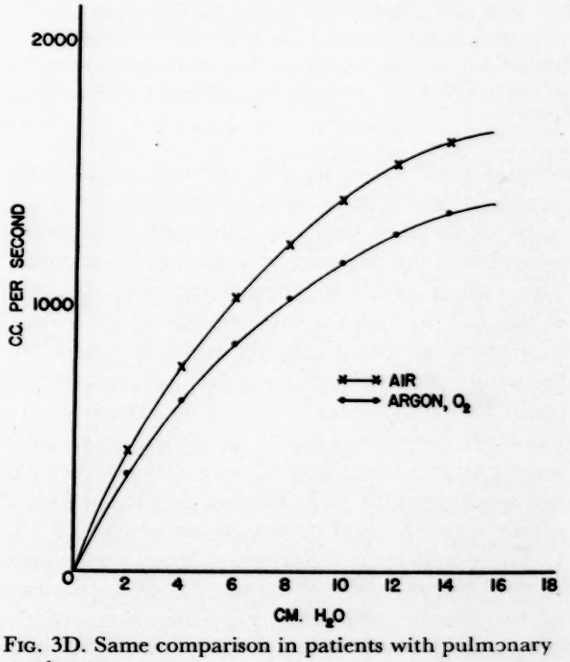


FIG. 3D. Same comparison in patients with pulmonary emphysema.

(Fig. 8B) and plotted against flow (Fig. 8C). This represents the second differentiation. The zero flow intercept in Figure 8C divided by two represents the value of the quadratic coefficient.

These calculations were carried out on the air and argon-oxygen pressure-flow curves of seven normal male subjects, five normal female subjects and seven male patients with pulmonary emphysema. The flow was expressed in liters per second and the pressure in centimeters of water. The values of these coefficients are given in Table I. The mean linear coefficient in normal subjects while breathing air was 1.50 and while breathing argon-oxygen was 1.87. The quadratic coefficient on air was 0.71 and on argon-oxygen was 0.99. The mean linear coefficient in emphysema patients breathing air was 6.04 and breathing argon-oxygen 7.12. The quadratic coefficient on air was 1.87 and on argon-oxygen was 2.50.

The coefficients determined from the experimental curves will be the complete coefficients of the linear term and quadratic term of the polynomial, $K_1Q + K_2Q^2 + \ldots$ If the tissue friction term, $f^{(Q)}_{tissue}$, has at least linear, (k_3Q), and quadratic, (k_4Q^2), terms, then the complete coefficient (K_1) of the linear term will be $(k_1\mu + k_3)$ and that for the quadratic term, (K_2), will be $(k_2\rho + k_4)$ in the limit of zero flow. The ratio of this coefficient when argon-oxygen is breathed as compared to air allows the estimation of the values of the tissue friction factor. For simplicity consider only the ratio of the linear coefficients,

$$\frac{(k_1\mu_{argon} + k_3)}{(k_1\mu_{air} + k_3)}$$

The value of this ratio, as k_3 becomes insignificant as compared to k_1, approaches the value of the ratio of the viscosities of the respective gases breathed. On the other hand, as k_1 becomes insignificant as compared to k_3, the value of this ratio approaches one. The same reasoning may be used for the quadratic terms.

These ratios were computed from the experimentally determined coefficients for each subject. The values appear in Table I. The experimentally determined ratios closely approach the ratio of the respective viscosities, 1.18, in the

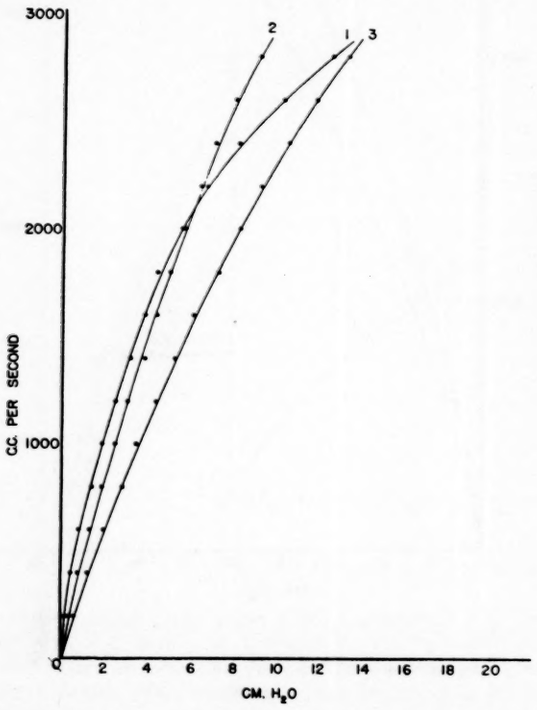


FIG. 4. Mean pressure-flow curves during inspiration in three normal subjects: (1) 1 L. above the functional residual volume; (2) at the functional residual volume; (3) 1 L. below the functional residual volume.

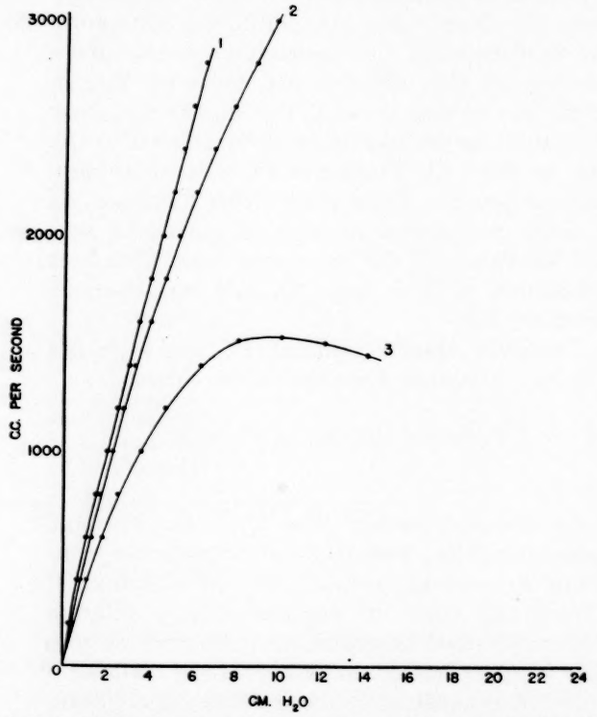


FIG. 5. Mean pressure-flow curves during expiration in three normal subjects: (1) 1 L. above the functional residual volume; (2) at the functional residual volume; (3) 1 L. below the functional residual volume.

case of the linear terms and the ratio of the respective densities, 1.33, in the case of the quadratic terms. This was found in both normal subjects and in the patients with emphysema. As reasoned heretofore, the conclusion to be drawn is that in both the normal subjects and the

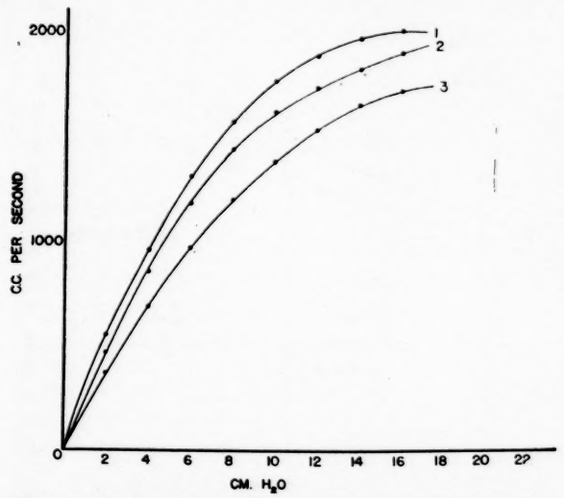


FIG. 6. Mean pressure-flow curves during inspiration in four patients with pulmonary emphysema: (1) 1 L. above the functional residual volume; (2) at the functional residual volume; (3) 1 L. below the functional residual volume.

patients with pulmonary emphysema who were studied, tissue friction is a negligible quantity.

COMMENTS

The problem of measuring the frictional resistance of the lung has been studied by several different methods in the past. The foundation for a theoretic understanding of the problem was first clearly defined by Rohrer.[9] His approach was based primarily on anatomic measurements of the respiratory tree. Assuming a rigid system of branching tubes, he calculated the resistance to air flow of this system using the measurements that he obtained from cadavers. From his calculations he was able to plot a pressure-flow curve. (Fig. 9.) It can be seen that this curve falls to the left of the experimental curve obtained in the present study. It is obvious that Rohrer's work was not intended as a method of measuring the resistance to ventilation. It was meant only to elucidate the physical principles involved.

Neergaard and Wirz[3] explored two methods of measuring the frictional resistance to ventilation experimentally in man. These were the alveolar pressure method and the intrapleural pressure method. The intrapleural pressure method, which was briefly mentioned earlier, is physiologically and physically the most valid approach. Neergaard and Wirz[3] measured the intrapleural pressure through a large-bore needle with a good optical recording system.

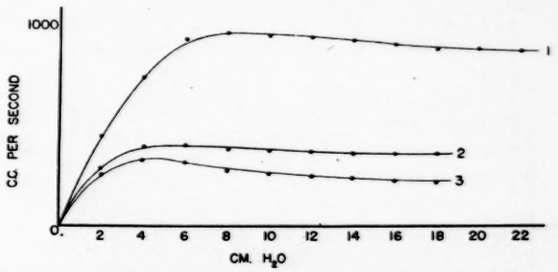
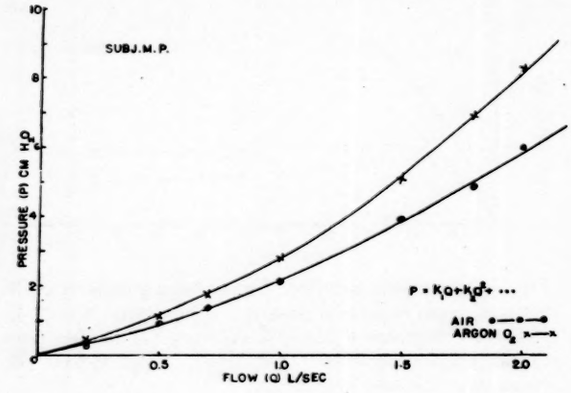


FIG. 7. Mean pressure-flow curves during expiration in four patients with pulmonary emphysema: (1) 1 L. above the functional residual volume; (2) at the functional residual volume; (3) about 1 L. below the functional residual volume.

Respiratory flow was recorded simultaneously from a pneumotachygraph. They were able to establish the lung elasticity curve by measuring the difference in intrapleural pressure at zero flow at the beginning and at the end of an inspiration. They subtracted the pressure produced by the retractive force of the lung from the total intrapleural pressure. This difference, as can be seen from equation 3, is the pressure required to overcome the tissue friction and gas flow resistance. This pressure was increased for a given level of flow as the subject breathed at progressively lower levels of lung inflation. In addition, they showed this pressure to be greater during expiration than during inspiration.

The alveolar pressure method consists of instantaneously interrupting the respiratory stream with some form of rapidly acting valve, such as an electrical solenoid shutter-type valve. At the instant of closure the pressure behind the valve will change from that of the oral cavity to that which must have existed in the alveoli. This equalization of pressure will occur extremely rapidly in normal subjects. This distinguishes the alveolar pressure from the more slowly changing pressure caused by the chest wall as it moves through the respiratory cycle. This method obviously includes only the pressure related to gas flow and not tissue friction. Neergaard and Wirz[3] and later Vuilleumier[14] used this method and compared it with the intrapleural pressure method. These investigators found that the alveolar pressure

method gave pressure-flow values which roughly corresponded to those obtained by the intrapleural pressure method. Otis and Bembower[15] and Proctor, Hardy and McLean[16] applied this method. The results of Otis and Bembower have been plotted with the data from Rohrer and from the present study. (Fig. 9.) Otis and Bembower found less resistance when the subjects breathed helium-oxygen mixtures or air at lower than atmospheric pressure. They were not, however, able to demonstrate change in resistance to flow at varying levels of lung inflation.



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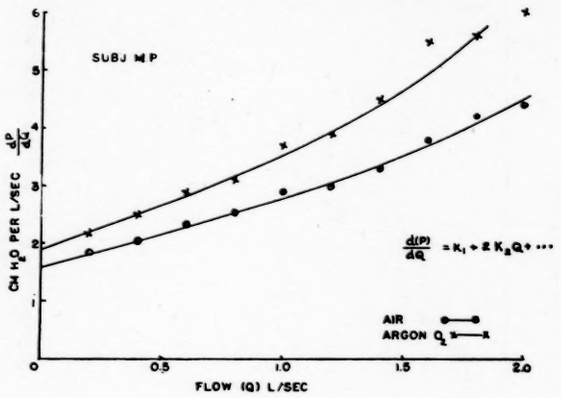

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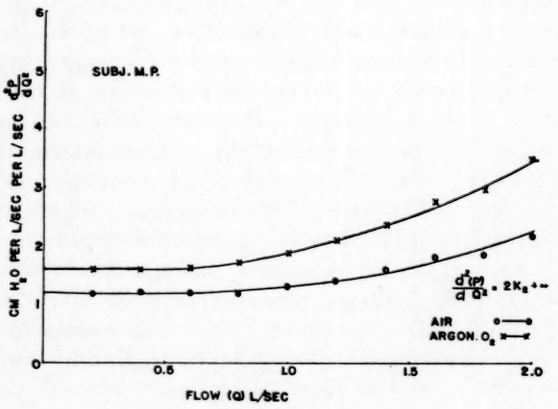


C

FIG. 8. The successive differentiation of the pressure-flow curves obtained breathing air and breathing argon-oxygen. A, the experimentally determined pressure-flow curves; B, the first derivative of these pressure-flow curves, C, the second derivative of these pressure-flow curves.

The fourth general approach to the problem has been made possible by the demonstration that intraesophageal pressure accurately reflects changes in intrathoracic pressure.[7,17,18] Mead,[19,20] using intraesophageal pressure as a measure of intrathoracic pressure and using integrating and subtracting circuits, was able to carry out electronically the tedious procedure of Neergaard and Wirz.[3] He placed the output of his computor, which would represent the pressure for tissue friction and gas flow resistance, on one axis of an oscilloscope and the rate of flow on the other. The trace thus obtained would be a pressure-flow curve. He found a mean pressure of 1.7 cm. of water was required to achieve a flow of 1 L. per second in normal subjects. (Fig. 9.) A greater pressure was required during expiration than during inspiration to produce the same respiratory flow. He showed that there was a severalfold increase in the pressure required to produce a given flow when the subject was breathing at a low level of lung inflation as compared with a normal or high level of inflation. He compared the alveolar pressure method with the intraesophageal pressure method and found the former method to give slightly higher values.

It can be seen that the portion of the intrathoracic pressure required to overcome tissue friction and the resistance to gas flow has been measured in a number of studies. Bayliss and Robertson[21] described a method of separating these two quantities in the lungs of cats. They estimated the amount of tissue viscance by com-

paring the pressure-flow relationships using air and hydrogen. The assumption was made that gas flow was entirely laminar and that no turbulence existed. These authors found that the tissue viscance was an important factor in resistance to movement of the lungs under the circumstances of their experiment. Dean and Visscher[22] repeated a similar set of experiments with dogs and showed that the major part of the tissue viscance was due to an adaptation of the lung to changes in volume. This is similar to mechanical hysteresis of an elastic body. McIlroy and Christie[23] attempted to separate viscous resistance of the lung tissue from gas flow resistance by studying human lungs obtained at postmortem. They used a method similar to Bayliss and Robertson. They concluded that tissue viscance was a major factor in the resistance to movement of the lungs under the circumstances of their experiment.

One of the chief purposes of the present study was to evaluate the various factors which contribute to the resistance to movement of the lungs of living human beings. There are three basic components which make up this resistance. These are: the pressure required to overcome the resistance to laminar gas flow, the pressure required to overcome the resistance to turbulent gas flow and the pressure required to overcome tissue friction. Each point on the pressure-flow curve represents the sum of these three pressures. As mentioned before, in a given system of ducts the portion of the flow that is laminar will have a pressure drop proportional to both the viscosity and the first power of the flow, while the portion of the flow experiencing eddying turbulence will have a pressure drop proportional to the density of the gas and square of the flow. The pressure required to overcome tissue friction is a function of the rate of flow and is independent of the

TABLE I

Subject	Sex	Age	Surface Area (M^2)	Vital Capacity (cc.)	Ratio of Residual Volume to Total Lung Volume	Linear Coefficient for Air (N_1)	Linear Coefficient for Argon-Oxygen (A_1)	$\frac{A_1}{N_1}$	Quadratic Coefficient for Air (N_2)	Quadratic Coefficient for Argon-Oxygen (A_2)	$\frac{A_2}{N_2}$
Normal Subjects											
W. S.	M	34	2.08	4800		1.66	2.06	1.24	0.56	0.78	1.39
C. B.	M	32	2.09	5200		0.86	1.02	1.19	1.20	1.65	1.38
M. P.	M	22	2.02	5400		1.58	1.85	1.17	0.63	0.85	1.35
A. W.	M	21	1.74	4100		1.12	1.30	1.16	0.90	1.12	1.24
R. B.	M	20	2.09	5150		0.94	1.23	1.30	0.39	0.60	1.54
R. B.	M	19	1.87	4500		1.68	2.25	1.34	0.61	0.79	1.30
F. B.	M	28	1.89	4000		1.15	1.45	1.26	0.28	0.39	1.39
C. L.	F	24	1.52	3100		1.89	2.36	1.25	0.70	0.92	1.31
M. L.	F	24	1.52	3200		1.80	2.08	1.16	0.56	0.94	1.67
J. B.	F	25	1.54	3100		1.08	1.72	1.59	0.69	1.02	1.48
M. J.	F	22	1.69	3600		1.96	2.40	1.22	1.09	1.47	1.35
E. A.	F	24	1.64	3600		2.26	2.70	1.19	0.90	1.40	1.56
Mean		24.6	1.81	4140		1.50	1.87	1.26	0.71	0.99	1.41
Emphysema Patients											
J. W.	M	63	1.88	3580	0.55	4.50	5.10	1.13	2.20	2.60	1.18
C. P.	M	59	1.68	2350	0.65	4.40	5.60	1.27	2.05	3.05	1.49
A. H.	M	60	1.47	2900	0.51	2.40	2.90	1.21	1.10	1.40	1.27
A. K.	M	58	1.89	3500	0.54	2.90	3.70	1.27	2.15	2.85	1.33
H. H.	M	61	1.68	2650	0.42	3.61	4.28	1.19	1.17	1.44	1.23
L. R.	M	58	1.89	3750	0.44	2.84	3.25	1.14	1.21	1.57	1.30
J. J.	M	66	1.56	1700	0.59	21.60	25.00	1.16	3.20	4.60	1.44
Mean		60.7	1.72	2920	0.53	6.04	7.12	1.20	1.87	2.50	1.32

gas breathed. It was possible to distinguish these three components by comparing the pressure-flow curve when the subject breathed air with that when he breathed argon-oxygen. The details of the mathematical analysis have been given. The conclusion obtained from these

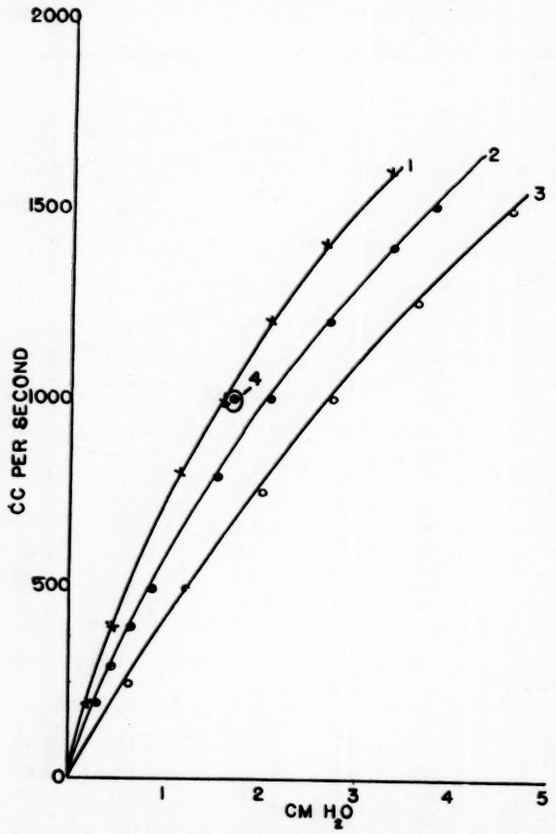


FIG. 9. Pressure-flow curves from normal human beings: (1) calculated curve of Rohrer;[9] (2) mean air pressure-flow curve from the present study; (3) pressure-flow curve of Otis and Bembower[15] using the intra-alveolar pressure method; (4) the mean pressure value for a flow of 1,000 cc. per second by Mead, Frank, Lindgren, Gaensler and Whittenberger.[20]

calculations is that all of the resistance to movement of the lungs can be attributed to laminar and turbulent gas flow. This means that tissue friction must be a negligible factor.

Pulmonary emphysema has been studied from many aspects but there are relatively few studies of the mechanics of ventilation in this disease. The first important study was by Neergaard and Wirz,[3] who used the intrapleural pressure method described earlier. Realizing the great hazard of inducing a pneumothorax in a person with emphysema, they were probably discouraged from studying any large numbers of these patients. In one patient with emphysema they observed a much higher resistance to ventilation of the lung than in two subjects without emphysema. They also noticed that the patient with emphysema had a much greater expiratory resistance than inspiratory resistance. Dayman[6] applied the method of Neergaard and Wirz in a larger number of patients with emphysema and found essentially the same results. In addition, he found that during expiration the rate of flow was slow and could not be increased in spite of large increases in intrapleural pressure. Similar results were found by Proctor, Hardy and McLean[16] using the alveolar pressure technic, and by Lindgren, Mead, Gaensler and Whittenberger[24] using the intraespohageal pressure method. It thus seems well established that emphysematous patients have markedly increased resistance to breathing.

The results of the present study also demonstrate an increased resistance to breathing in pulmonary emphysema. The resistance is increased both during inspiration and expiration, especially the latter. Mathematical analysis of the inspiratory pressure-flow curves revealed that both laminar and turbulent flow resistance for the group of emphysema patients were increased approximately threefold as compared with the group of normal subjects. Calculations derived from the comparison of the air and argon-oxygen pressure-flow curves revealed that tissue friction was negligible in emphysema as in normal subjects. This is in conflict with the conclusions of McIlroy and Christie[25] derived from a study of emphysematous lungs obtained at postmortem.

The means by which resistance to air flow is increased in patients with pulmonary emphysema is of interest and importance. It has generally been assumed that emphysema is associated with obstruction of the bronchioles.[26] The frequent association of pulmonary emphysema with bronchial asthma and chronic bronchitis is well known. Moreover, patients with emphysema have great difficulty in clearing their bronchial tree of retained secretions because of impairment of the effectiveness of the cough.

Another important and perhaps less well appreciated cause of increased resistance to air flow is unequal ventilation of various portions of the lung. Numerous studies have shown that there is unequal ventilation of the alveoli in emphysema.[27,28] The reason for this is apparent.

The loss of elasticity of the lung is unequally distributed throughout the lung parenchyma. This is shown by the formation of bullae. The less elastic portions of the lung will fill with air early in the inspiratory cycle while those portions retaining more elasticity do not fill until later. Thus there will be rapid flow in some bronchioles and almost no flow in others at any given time. Moreover, some of the small bronchi or bronchioles may be obstructed by accumulated secretions or pathologic changes in their walls. This may result in air reaching a portion of the lung by the process of collateral ventilation.[29]

A striking finding in patients with emphysema is the relationship between the volume of the lung and the resistance to air flow. (Figs. 6 and 7.) This effect is most marked during expiration. In the normal person (Figs. 4 and 5) the resistance to air flow during expiration is several times greater when the lung volume is slightly above the residual volume than when the lung is almost completely inflated. This difference is even more striking in patients with pulmonary emphysema (Fig. 7) where at all degrees of inflation of the lung the expiratory pressure-flow curve tends to reach an asymptote. In other words, a maximum flow is achieved above which further increases in pressure result in no change in flow. At lung volumes near the residual volume the maximum flow which can be attained is much lower than at volumes near maximum inspiration.

In considering the reason for this relationship it is necessary to describe the anatomy of the bronchioles and the forces which influence their diameter. The basic anatomic unit of the lung consists essentially of an elastic expansile portion communicating with the rigid cartilage-invested bronchial tree through an unsupported terminal bronchiolar system. It is this unsupported portion of the bronchial tree which is of particular importance in the pathologic physiology of pulmonary emphysema. A model devised to simulate the function of the basic pulmonary unit is shown in Figure 10. The unit is placed in a cylinder with a piston. Movement of the piston produces volume and pressure changes which represent those of the thoracic cavity. The elastic pressure, P_L, is a function of the amount of distention of the alveolus. Under static conditions the intrathoracic pressure, P_T, equals P_L. Under dynamic conditions, that is when the piston is moving, the intrathoracic pressure, P_T, is equal to the sum of P_L plus the pressure, P_P, required to produce gas flow along the bronchiole. Now let us consider the forces acting on the bronchiole at point "B." For purposes of simplicity in discussing the pressure relationship in the model, the pressure in the bronchiole

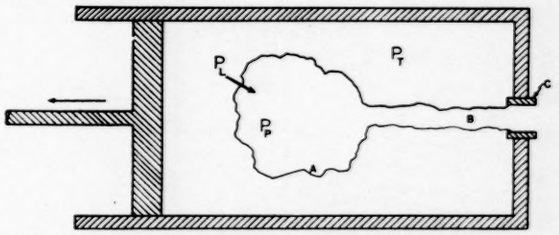


FIG. 10. A model simulating the basic pulmonary unit; A, expansile elastic unit; B, unsupported bronchiole; C, rigid bronchus; P_T, pressure in cylinder; P_L, elastic pressure of expansile unit; P_P, pressure in expansile unit.

at point "B" should be considered to be approximately atmospheric. This is not true in the lung, since the pressure at "B" is equal to the pressure drop between this point and the atmosphere. However, this in no way alters the principles involved. In the model, the pressure acting on the bronchiole at "B" will be equal to P_T. Consequently, during inspiration this pressure will always be negative. Its magnitude will depend on the degree of distention of the alveolus and upon the rate of flow. During expiration P_T will be negative until P_P exceeds P_L, at which time P_T becomes positive. This point is extremely important since previously the pressure, P_T, tended to distend the bronchiole whereas now P_T tends to collapse the bronchiole.

Transferring these simple concepts to the human lung, the relationship between pressure, flow and amount of distention of the lung can be more clearly defined. The character of the pressure-flow curve is dependent on the degree of inflation of the lungs. This is because the retractive force of the lungs is dependent on the degree of inflation. Consequently, the intrathoracic pressure will be more negative with the chest in the inspiratory position than with the chest in the expiratory position. The distending pressure in the bronchioles and hence the diameter of the bronchioles will be greater in the inspiratory position than in the expiratory position.

As noted before, the relationship between the position of the chest and the pressure-flow curves is more striking in emphysema than in normal subjects. This is related to the alteration of the

elastic properties of the lungs[8] and to the increased resistance to air flow in emphysema. In the expiratory position of the chest the retractive force of the lung and hence P_L become small. The intra-alveolar pressure, P_P, during expiration is large because of the increased resistance to air flow, and as a consequence the intrathoracic pressure becomes positive.

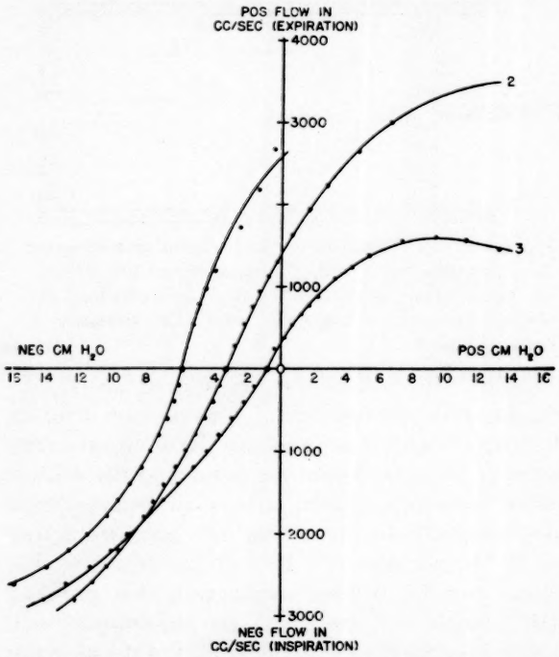


FIG. 11. Mean pressure-flow curves during inspiration and expiration obtained from three normal subjects (Figs. 4 and 5) replotted according to intrathoracic pressure, P_T, instead of $P_T - P_L$: (1) 1 L. above the functional residual volume; (2) at the functional residual volume; (3) 1 L. below the functional residual volume.

If during expiration the intrabronchiolar pressure increased to the same degree as the intrathoracic pressure, the net effect on the diameter of the bronchioles would be negligible. This occurs in laryngeal obstruction. In emphysema, however, the increased resistance to air flow is at the bronchiolar level. As a consequence, there is a large pressure drop between the alveolus and the bronchial end of the unsupported bronchiole. Therefore the increase in intrathoracic pressure is not accompanied by a corresponding increase in intrabronchiolar pressure, and as a result the bronchiole tends to be collapsed. This mechanism has been described by Dayman[6] and Neergaard and Wirz.[3]

The pressure-flow curves which were obtained at three different levels of lung inflation were plotted as intrathoracic* pressure against flow. The continuous curves obtained are illustrated in Figures 11 and 12. Expiratory flow is above and inspiratory flow below the horizontal axis. Negative intrathoracic pressure is to the left and positive to the right of the vertical axis.

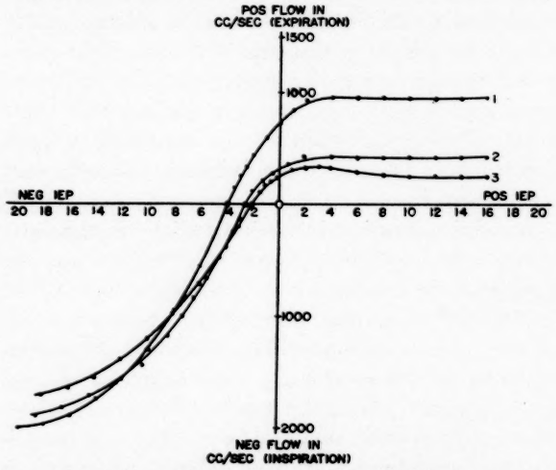


FIG. 12. Mean pressure-flow curves during inspiration and expiration obtained from four patients with emphysema (Figs. 6 and 7) replotted according to intrathoracic pressure, P_T, instead of $P_T - P_L$: (1) 1 L. above the functional residual volume; (2) at the functional residual volume; (3) 1 L. below the functional residual volume

The striking feature of these curves may be seen by observing that the expiratory curves begin to curve rapidly toward an asymptote at approximately the same intrathoracic pressure. This shows clearly the dependence of the bronchiolar diameter and thus resistance to gas flow on the intrathoracic pressure.

The other point to observe from these curves is that the intercept that each curve makes with the horizontal axis represents the intrathoracic pressure at zero flow. This is the retractive force, P_L, of the lung at that particular level of lung inflation. Therefore each of these intercepts represents a point on the lung elasticity curve.

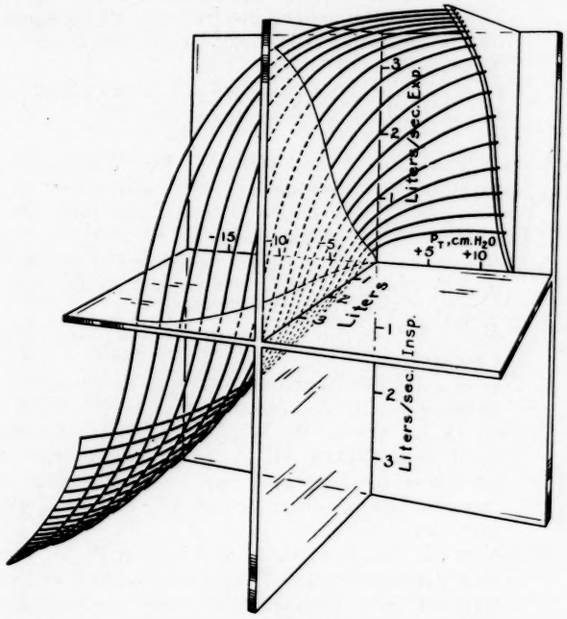
This suggests a way of plotting the three variables, flow, volume and intrathoracic pressure, by using a three-dimensional graph so that the functional interrelationships may be more easily seen. (Figs. 13 and 14.) The pressure and flow axes are the same as in the preceding two-dimensional graphs. (Figs. 11 and 12.) The

* Intraesophageal pressure was used as a measure of intrathoracic pressure. As mentioned under Method, intraesophageal pressure was measured with respect to intraoral pressure.

added dimension is the volume axis. This axis represents the vital capacity.

The pressure-flow curves are plotted on this three-dimensional graph. As these curves were measured at a constant lung volume, each curve will lie in a plane which is perpendicular to the volume axis. The intercept of the curves with the horizontal or zero plane will represent the lung elasticity curve. A surface is thus formed by successive pressure-flow curves. This surface represents the plot of equation 1.

The three-dimensional diagram illustrates the defects in the mechanics of ventilation in pulmonary emphysema. The key to the problem lies in the fact that if the retractive force of the lung is exceeded by the pressure drop needed to produce gas flow from the alveolus to the cartilaginously supported bronchi, a net pressure tending to produce attenuation of the bronchiole is developed. In emphysema the alteration in the normal retractive force of the lung and the increased resistance to air flow in the bronchiole permits the development of positive intrathoracic pressure during expiration at a relatively low rate of air flow. In order to diminish the increased bronchiolar resistance to gas flow associated with pulmonary emphysema the lung must be maintained in a state of greater inflation, thus increasing the magnitude of the retractive force of the lung.



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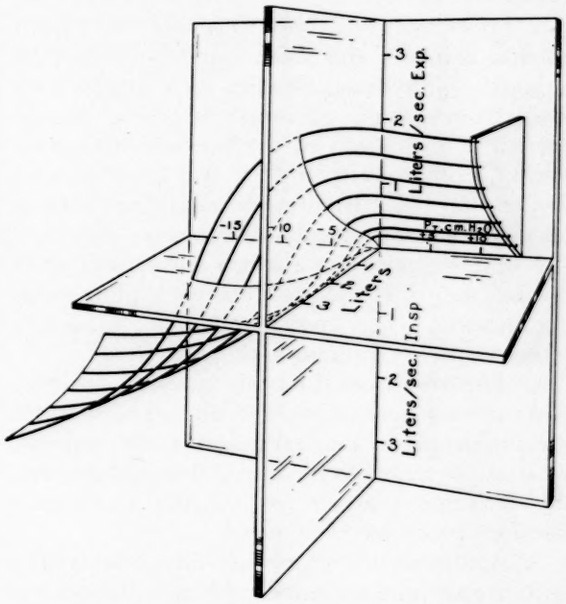

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FIG. 13. Three-dimensional diagram relating intrathoracic pressure, P_T, respiratory flow on inspiration and expiration and vital capacity in normal subjects. The vertical axis represents expiratory flow above the horizontal plane and inspiratory flow below. The horizontal axis extending from right to left represents intrathoracic pressure. The other horizontal axis which projects toward the reader represents the vital capacity. The successive pressure-flow curves from a surface which is the locus of the equation, $P_T = P_L + P_P$. The intercept of the pressure-flow curves with the horizontal plane is the lung elasticity curve. Three of these pressure-flow curves were obtained from the experimental data (Figs. 11 and 12). The others are theoretical.

FIG. 14. Three-dimensional diagram relating intrathoracic pressure P_T, respiratory flow on inspiration and expiration and vital capacity in patients with emphysema.

These findings explain the limitation of maximum breathing capacity and one-second vital capacity in pulmonary emphysema. In these tests of pulmonary function the subject attempts to achieve maximum rate of air flow. As a consequence the rate of flow achieved during expiration will be defined by the pressure-flow asymptote for each position of the chest. The volume of air expired during a given period of time will be the integral of the time-flow curve.

SUMMARY

1. The intrathoracic pressure exclusive of the pressure required to overcome the retractive force of the lung was measured and shown to be functionally related to the rate of respiratory flow in both normal and emphysematous subjects. This pressure increment at any given level

of flow represents the pressure required to overcome both the resistance to air flow through the bronchopulmonary passages and the frictional resistance of the intrathoracic tissues to deformation. The resistance to gas flow is composed of resistance to laminar gas flow and resistance to turbulent gas flow.

2. Pressure-flow curves were obtained from normal subjects and from patients with pulmonary emphysema. Studies were made with subjects breathing air and breathing argon-oxygen. Comparison of the pressure-flow relationships obtained with these two gases demonstrated that tissue friction was negligible both in normal and emphysematous subjects.

3. The resistance to gas flow was evaluated in normal subjects and patients with pulmonary emphysema. The resistance was markedly increased in the patients with emphysema.

4. The resistance to both laminar gas flow and the resistance caused by eddying turbulence are important in normal subjects and patients with emphysema. As the rate of flow is increased, the resistance caused by eddying turbulence becomes progressively greater.

5. A change in the pressure-flow relationship with change in the amount of lung inflation was demonstrated. This was observed particularly during expiration. More pressure was required to produce a given flow at lesser degrees of lung inflation. This was marked in emphysematous subjects. The three variables, pressure, flow and lung inflation, were expressed on a three-dimensional graph.

6. During expiration in emphysematous subjects the pressure-flow curve bends rapidly to approach an asymptote of flow. This accounts for the inability of patients with emphysema to exceed a certain flow regardless of the pressure exerted. In emphysema there is an increase in resistance to air flow in the bronchioles and a decrease in the elastic force of the lung for a given degree of inflation of the lung. As a result, collapse of the unsupported bronchioles tends to occur when the pressure drop between the alveoli and the cartilaginously supported end of the bronchiole exceeds the elastic pressure of the lung.

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Seminars on Liver Disease

Liver Disease—Morphologic Considerations*

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THE morphologic alterations of the liver in disease have recently become of compelling interest to the clinician since, with liver biopsy now generally available as a clinical tool, the understanding of such changes may be directly applicable to management of the patient. A mass of partially conflicting single observations in this field is gradually becoming organized into a unified concept but a systematic classification of liver disease based upon coordinated use of clinical, physiologic and pathologic findings, such as has been accomplished in renal disease, still remains to be developed. The present review attempts to summarize the progress which has been made in this direction.

NORMAL ANATOMY OF THE LIVER

The principal unit of the liver is the epithelial liver cell. Its histochemical characteristics reveal the presence of components such as fat, glycogen, iron, enzymes (including phosphatase, esterase and oxidizing enzymes)[1,2] and vitamin A,[3] which mirror some of the functions of these cells. The marked cytoplasmic basophilia, a feature common to cells capable of marked protein formation,[4,5] is due to the presence of pentose nucleic acids, stainable with pyronine, demonstrable by spectrophotometry and specifically removed by the enzyme ribonuclease.[6,7] The cytoplasmic basophilia of the liver cells apparently reflects their ability to form serum albumin[8] and other proteins.

Re-investigation of the structure of the normal liver[9] (Fig. 1) has revealed that it consists of a system of plates of epithelial liver cells, each one-cell in thickness. These plates are curved and meet at various angles to surround an irregularly ramified labyrinthine cavity. The arrangement of the plates varies, depending upon the flow of blood and the blood pressure gradient within the lobules.[10] Alteration of this gradient, for example by passive congestion, almost reverses the lobular pattern. In human embryos as well as in adult lower animals these plates are two or more cells thick[11,12] and the same increase in thickness may be found in adult man during regeneration or hepatoma formation.

The bile capillaries are in grooves between the epithelial cells, presumably as an adaptation of their cell membranes. They communicate with each other to form a chicken-wire meshwork within the liver cell plates[9] and continue into the bile ductules (cholangioles) which are lined with epithelial cells differing structurally and cytochemically from the liver cells. These ductules develop from the liver cells embryologically[13] and in exaggerated fashion during abnormal processes, especially in regeneration. The ductules form intercommunicating loops within the lobular parenchyma[9] but are found in greater number around the portal triads where they break through the continuous cylinder of liver cells, the limiting plate,[9] which separates the lobular parenchyma from the portal triad. In the portal triads the ductules (here often called septal bile ducts[14,15]) combine to form the interlobular bile ducts which drain the bile from the liver.

The sinusoids are in the hepatic labyrinth between the liver cell plates; they differ from other capillaries in being more permeable to serum proteins and by incorporating special endothelial cells, the Kupffer cells. All of them are capable of the same functions although they do not all perform these activities simultaneously.[16] These are the functions of the reticuloendothelial system, such as phagocytosis, blood pigment breakdown and probably also antibody formation. The sinusoids are separated

* From the Hektoen Institute for Medical Research, and the Departments of Pathology of Cook County Hospital, and Northwestern University Medical School, Chicago, Ill. Supported by a grant from the Dr. Jerome D. Solomon Memorial Research Foundation.

from the liver cells by a narrow tissue space (Disse space) which is traversed by reticulum fibers and is normally almost obliterated. The blood coursing through the sinusoids (in an opposite direction to the bile flow) is derived largely from the portal vein. Due to streamlines of flow in the main portal stem the right hepatic lobe receives blood rich in nutrients mainly from the superior mesenteric vein whereas the left lobe receives blood chiefly from the inferior mesenteric and splenic veins.[17,18] The hepatic artery exhibits greater variations in its extrahepatic and intrahepatic portion than any other major artery,[19] which explains the great difference in the morphologic consequences of its ligation.[20] The hepatic artery not only delivers its blood into the portal canal but also directly to all zones of the parenchyma within the lobules through intralobular arterioles, which are often accompanied by bile ductules.[21] Sphincter action of the intralobular arterioles, similar to that of the inlet and outlet veins,[16] is responsible for variations in the arterial blood supply.

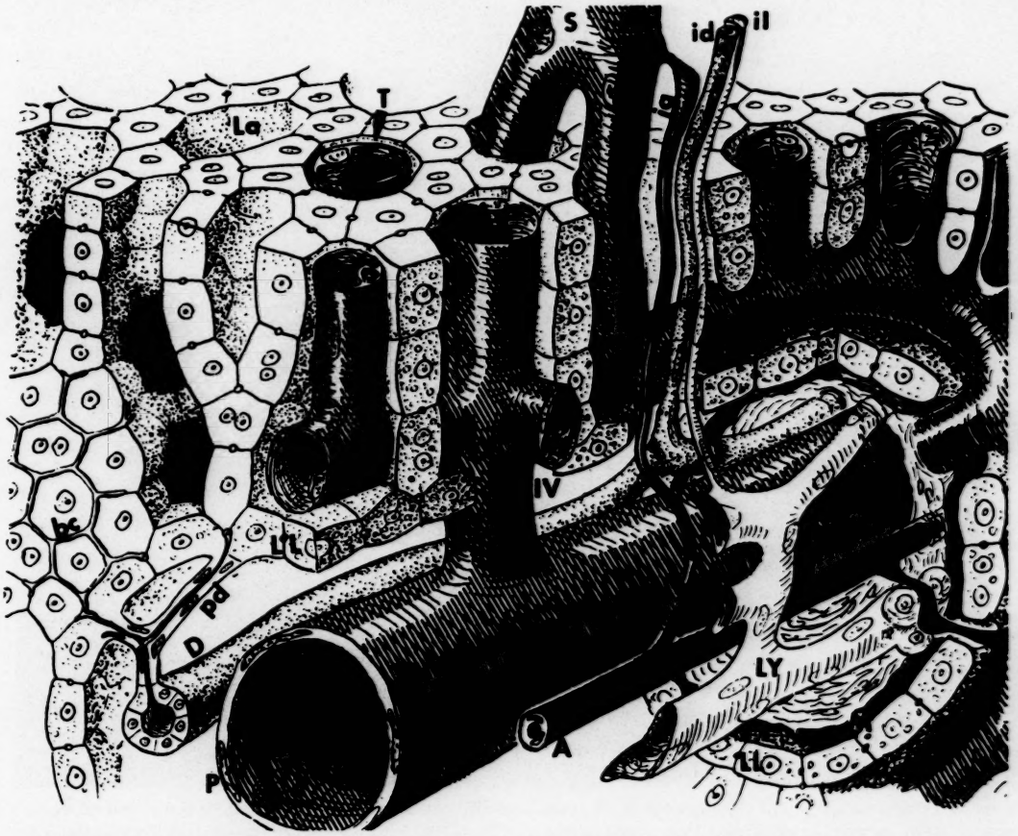


FIG. 1. Stereogram of the normal liver (drawn by Hans Elias). A, hepatic artery branch; bc, bile capillary; D, interlobular bile duct; ia, intralobular arteriole; id, intralobular ductule (cholangiole); il, intralobular lymph vessel; IV, inlet venule; K, Kupffer cell; La, labyrinth; LL, limiting plate; LY, portal lymph vessel; P, portal vein branch; pd, periportal ductule; S, sinusoid; T, tissue space of Disse.

RELATION OF HISTOLOGIC FINDINGS IN LIVER BIOPSY SPECIMENS TO THOSE AT NECROPSY

The relatively small needle biopsy specimen is not always representative of the entire liver in respect to inflammatory and fibrotic changes although it does reflect well diffuse liver cell damage or diffuse fatty metamorphosis.[22] Needles wider than the usually applied Vim-Silverman instrument increase the chances of finding focal lesions such as tubercles, Boeck sarcoid follicles or carcinoma metastases, especially since focal nodules may be clearly visible on gross inspection.[23] The danger of hemorrhage due to low prothrombin activity makes liver biopsy too hazardous in severe liver disease. This leaves a gap in our knowledge since the necropsy specimen reveals additional changes developing in the agonal period and as a result of postmortal

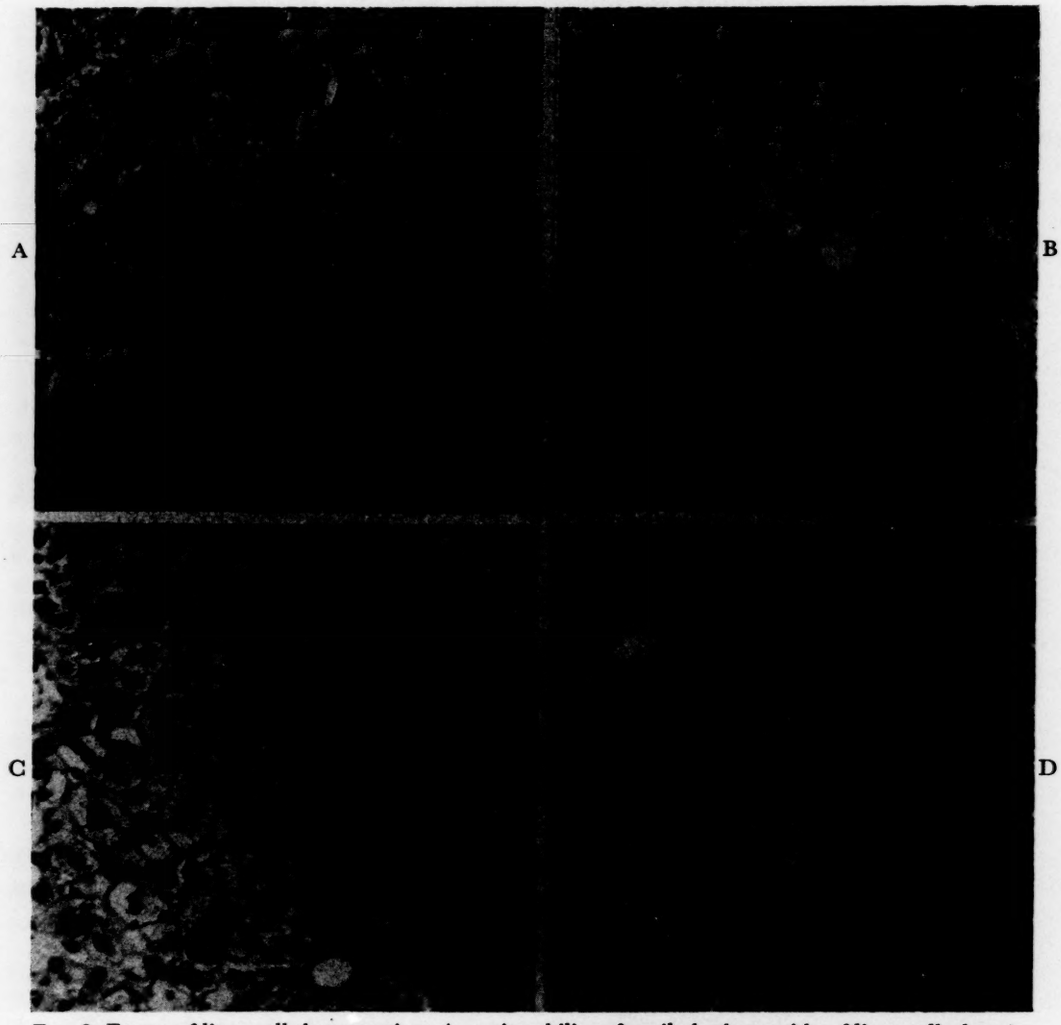


FIG. 2. Forms of liver cell degeneration. A, eosinophilic refractile body outside of liver cell plate in acute viral hepatitis; diffuse liver cell damage (× 230). B, clumps of coagulated cytoplasmic protein in toxic hepatitis (× 230). C, focal plant cell–like appearance of liver cells due to anoxia in extrahepatic biliary obstruction (× 190). D, "feathery" degeneration of liver cells near bile plugs in lobular center in early biliary obstruction due to carcinoma of pancreas (× 150).

autolysis. In the moribund patient the hepatic circulation fails, much as in shock; this produces centrolobular necrosis not related to the specific liver disease itself. Liver biopsy specimens therefore often fail to show changes seen in the subsequent postmortem specimen.[24–26] In the agonal period glycogen disappears from the liver cells and increased permeability of the sinusoidal wall for protein results in a widening of the tissue spaces which become filled with proteinic debris.[25] This terminal edema has been wrongly interpreted as a serous hepatitis. There is, however, an intravital serous hepatitis[27–29] though probably of less significance than previously thought. Quite often the liver cell plates become fragmented in the agonal or postmortal period, especially if the liver cells are damaged. This dissociation of the liver cells reported in the older literature and considered to be the cause of parenchymal jaundice[30] has only in exceptional instances a true counterpart in the living liver.[24,25]

RELATION BETWEEN MORPHOLOGIC CHANGES AND THE RESULTS OF HEPATIC TESTS

Liver biopsy provided the opportunity to rectify the misleading agonal changes found in the cadaver liver and to correlate histologic alterations with clinical findings. However, the results have been disappointing in that severe hepatic failure sometimes has been found asso-

ciated with relatively few histologic changes while, on the other hand, apparently intact liver function may be combined with widespread changes of the hepatic parenchyma. This is due in part to the fact that hardly any of the hepatic tests in use measure a basic function of the liver,[31] in part to the ability of a small segment of the liver to carry on most of its function,[32] and in part to the marked regenerative ability of the liver which makes it difficult to judge the function of altered liver cells. Attempts to establish a good correlation between the histologic picture of specific liver disease and the clinical and laboratory findings have usually failed.[33–35] Somewhat better results were obtained if individual physiopathologic features were used for correlation.[36–38] Even here, such correlations as were found represent only trends at best since they were based on statistical analysis of a larger number of cases, with many exceptions in individual cases.

PHYSIOPATHOLOGIC FEATURES IN LIVER DISEASE

It therefore appears advantageous for the understanding of the functional disorders of the liver to discuss the appearance, etiologic factors and functional correlation of the individual features which in various combinations produce the morphologic picture of liver disease.

Liver Cell Degeneration. Liver cell degeneration may take different forms such as acidophilic degeneration due to loss of the basophilic cytoplasmic nucleic acids. This loss may precede nuclear changes and seems to be the first morphologically recognizable alteration of the liver cell.[8,39,40] It may progress to apparent coagulation of the cytoplasm and the resulting "hyalinization" may either be homogeneous, leading to the acidophilic bodies (Councilman bodies) (Fig. 2A) found very commonly in hepatotropic virus diseases such as viral hepatitis,[26,41,42] yellow fever[43] and dog hepatitis,[44] or it may take the form of small clumps which are arranged around the nucleus in a rarified cytoplasm (Mallory bodies in alcoholic cirrhosis,[45] but found also in other lesions). (Fig. 2B.) Another type of liver cell degeneration is hydropic swelling which gives the cell the appearance of plant cells, with rarified cytoplasm and sharp borders. (Fig. 2C.) Such lesions are seen in experimental animals[46] and in aviators[47,48] exposed to low atmospheric pressure and can be considered characteristic of local hypoxia. They are also found in intoxications such as carbon tetrachloride[49] or bromobenzene[50] poisoning, (Fig. 5D) although under such circumstances local respiratory deficiency due to circulatory or enzymatic disturbances may be responsible. In severe bile stasis, liver cells loaded with bile pigment or in proximity to bile plugs have a rarified cytoplasm in which there is a fine brown pigmented protoplasmic network (feathery degeneration).[51] (Fig. 2D.) Fatty metamorphosis is sometimes also an expression of degeneration since it is produced by toxic agents (e.g., carbon tetrachloride, chloroform, mushrooms, phosphorus) or milder hypoxia.[52] This will be discussed in greater detail later.

From the point of view of liver function, the extent of the lesion, whatever its histologic appearance, is of paramount importance. Involvement of only small parts of the lobule, as in central acidophilic degeneration in early congestion or in focal hydropic swelling, causes no functional manifestations. Diffuse involvement of the lobule (characterized by variations in staining qualities of nucleus and cytoplasm) coincides usually with functional changes. Statistically, the extent of liver cell damage is significantly correlated with the degree of positive results in cephalin flocculation and thymol turbidity tests, increase in total and direct bilirubin, decrease in serum albumin and increase in serum globulin. Increase of the alkaline phosphatase activity and of the urinary urobilinogen excretion has been found associated qualitatively but not quantitatively with liver cell damage.[37]

Atrophy is characterized by thinning of the liver cell plates. If it is the result of debilitating disease, senility or starvation, it is associated with deposition of wear-and-tear pigment but produces little functional impairment. In atrophy due to slight compression, as in the earlier stages of bile or blood stasis, the cytoplasmic basophilia is increased, without evidence of functional impairment. However, with severe generalized compression of the liver cell plates, as in amyloidosis, the basophilia disappears[40] and there is functional impairment. (Fig. 6D.) Focal atrophy near space-occupying lesions (tumors or abscesses) apparently does not affect hepatic function.

Hepatocellular Necrosis. This represents an advanced degree of degeneration characterized by loss of nuclear staining and eventual disappearance of the whole cell. Again the extent of the lesion determines the functional impairment.

Focal necrosis is the death of one or several cells. It may occur scattered throughout the lobule and usually attracts scavenger cells (segmented leukocytes and later lymphocytes), the accumulation of which is more striking than the disappearance of liver cells. (Fig. 3A.) If the associated with functional signs of liver cell damage.

Central necrosis involves all cells in the centrolobular zone.[54,55] (Fig. 3B.) Fragments of necrotic liver cells may be present as anuclear structures often revealing a granular coagulated

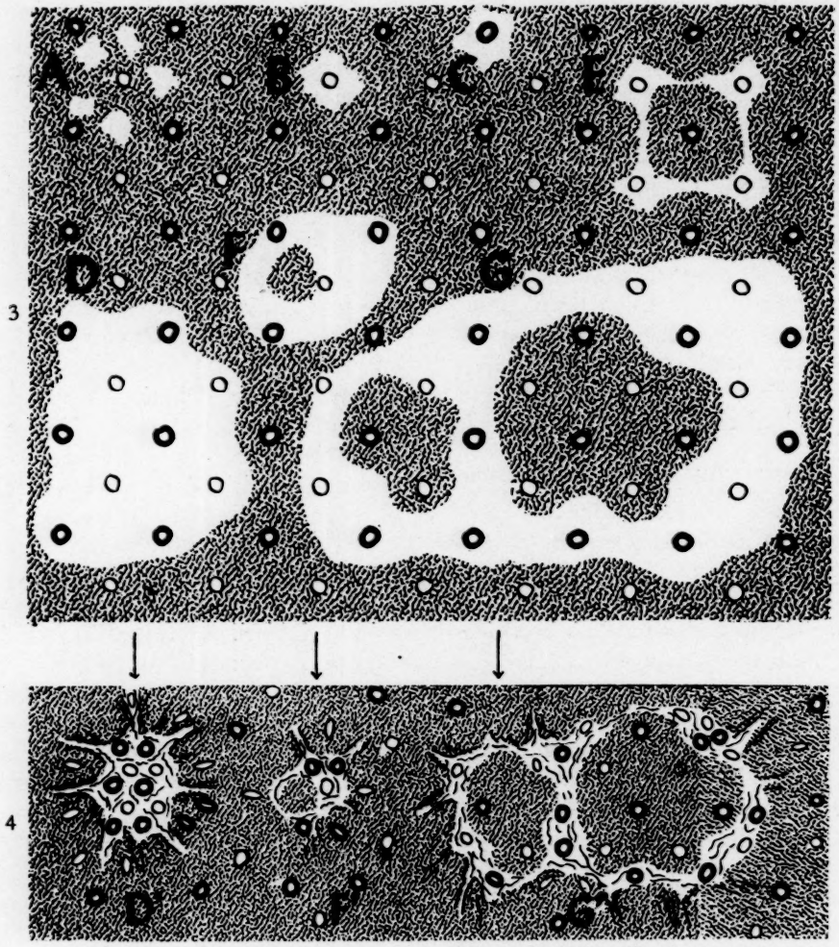


FIG. 3. Diagram of types of hepatic necrosis (drawn by Hans Elias). Portal canals, heavy circles; central fields, light circles. A, focal necrosis; B, central necrosis; C, periportal necrosis; D, massive necrosis. Submassive necrosis: E, central bridging; F, remaining fragment of lobule; G, multilobular fragments.

FIG. 4. Diagram of types of collapse (drawn by Hans Elias). Portal canals, heavy circles; central fields, light circles. D′, following massive necrosis; F′ following submassive necrosis, the nodules being fragments of one lobule; G′ multilobular nodules.

surrounding liver cells are normal (Fig. 5A) no functional impairment is noted despite the conspicuous morphologic changes.[36] The necrosis of scattered single cells characteristic of viral hepatitis is associated with hepatocellular degeneration of the rest of the lobular parenchyma producing, at least at the peak of the disease, "spotty necrosis"[24,26,41,42,53] (Fig. 5B) which is cytoplasm. (Fig. 5C.) The liver cells which have disappeared are either replaced by red cells and a few scavenger cells or the framework may collapse. This lesion is found in circulatory insufficiency in the lobule caused by congestion[55] or shock[56,57] or hepatic artery ligation.[20] As a hypoxic phenomenon it becomes most apparent where the oxygen saturation of the sinusoidal

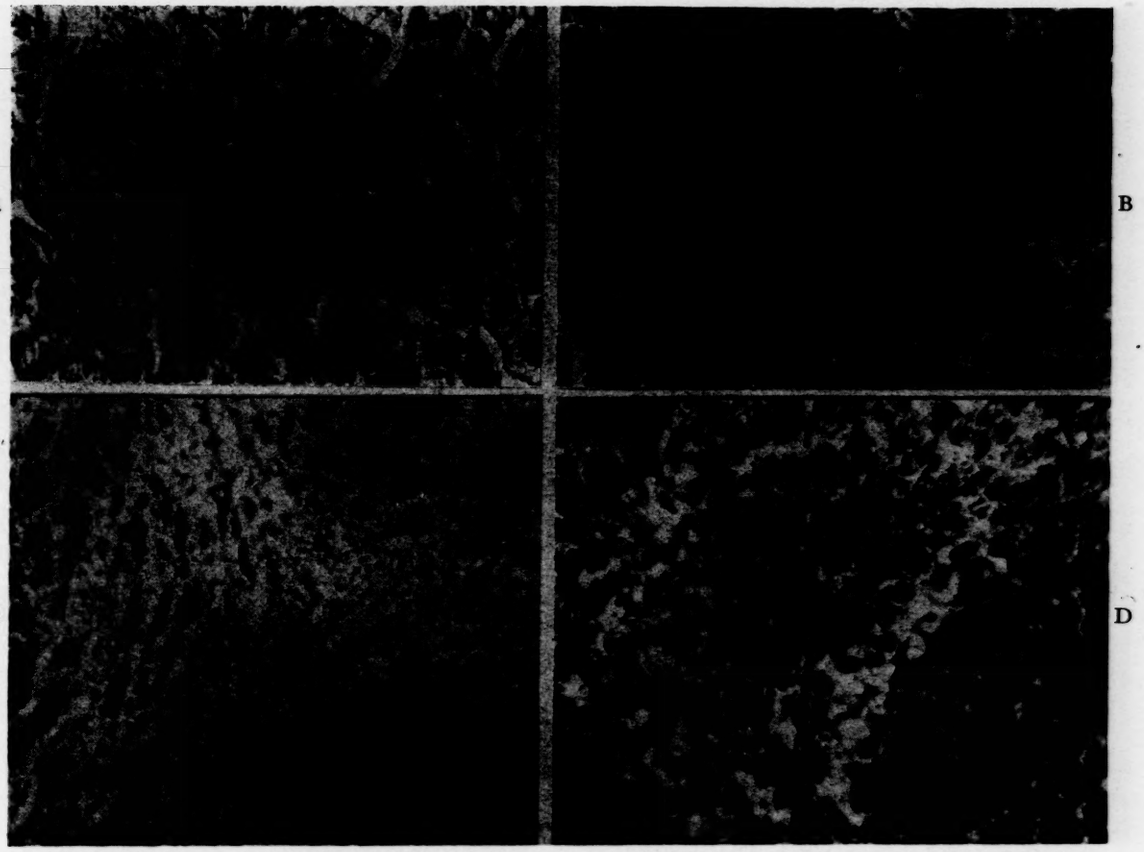


FIG. 5. Forms of hepatocellular necrosis. A, focal necrosis in non-specific reactive hepatitis due to tuberculosis; liver cell remnants removed by segmented leukocytes; surrounding liver cells normal (× 285). B, "spotty" necrosis in acute viral hepatitis; accumulation of round cells in place of liver cells which have disappeared; the surrounding parenchyma reveals liver cell degeneration and great variation of neighboring cells (× 350). C, central necrosis in carbon tetrachloride intoxication; liver cell fragments remain in the collapsed zone which reveals little cellular reaction (× 80). D, central necrosis of rat intoxicated with bromobenzene; central accumulation of scavenger cells surrounded by a zone of liver cells with hydropic swelling (× 80).

blood is lowest. In toxic conditions the localization of the necrosis is probably also a reflection of oxygen want due either to swelling of the cells on the periphery of the lobules interfering mechanically with circulation[18,59] or to interference with oxidative enzymes.[58] (Fig. 5D.) Central necrosis is a typical postmortem lesion rarely seen in biopsy specimens. Its relation to functional impairment is variable, depending upon the status of the non-necrotic parenchyma. Mid-zonal necrosis is rarely found in man.[60]

Massive (sub-massive) necrosis: Quite often central necrosis may extend at least in some areas, to the periphery of the lobule (sub-massive necrosis). (Fig. 6B.) Contiguity with necrotic areas of neighboring lobules results in bridge formation. (Fig. 3E.) Sometimes all cells of lobules become necrotic (massive necrosis). (Fig. 3D.) As in zonal necrosis liver cell fragments intermixed with scavenger cells may still be present or may disappear. After a period in which red cells fill the spaces previously taken up by the liver cells, the framework which has thus been held intact collapses. In massive collapse one or several lobules become small "ghost lobules" with closely approximated portal and central canals. (Fig. 4D.) In sub-massive collapse lobular fragments of different size and shape persist. (Figs. 3F, 3G, 4F and 4G.) Massive necrosis involving the greater part of the liver simultaneously is rapidly fatal.[61] (Fig. 6A.) Isolated foci of massive necroses may be tolerated without serious interference with hepatic function.

Anoxic necrosis: The hypoxia in zonal, massive or sub-massive necrosis does not injure the less sensitive framework or the Kupffer and other mesenchymal cells. They become necrotic only

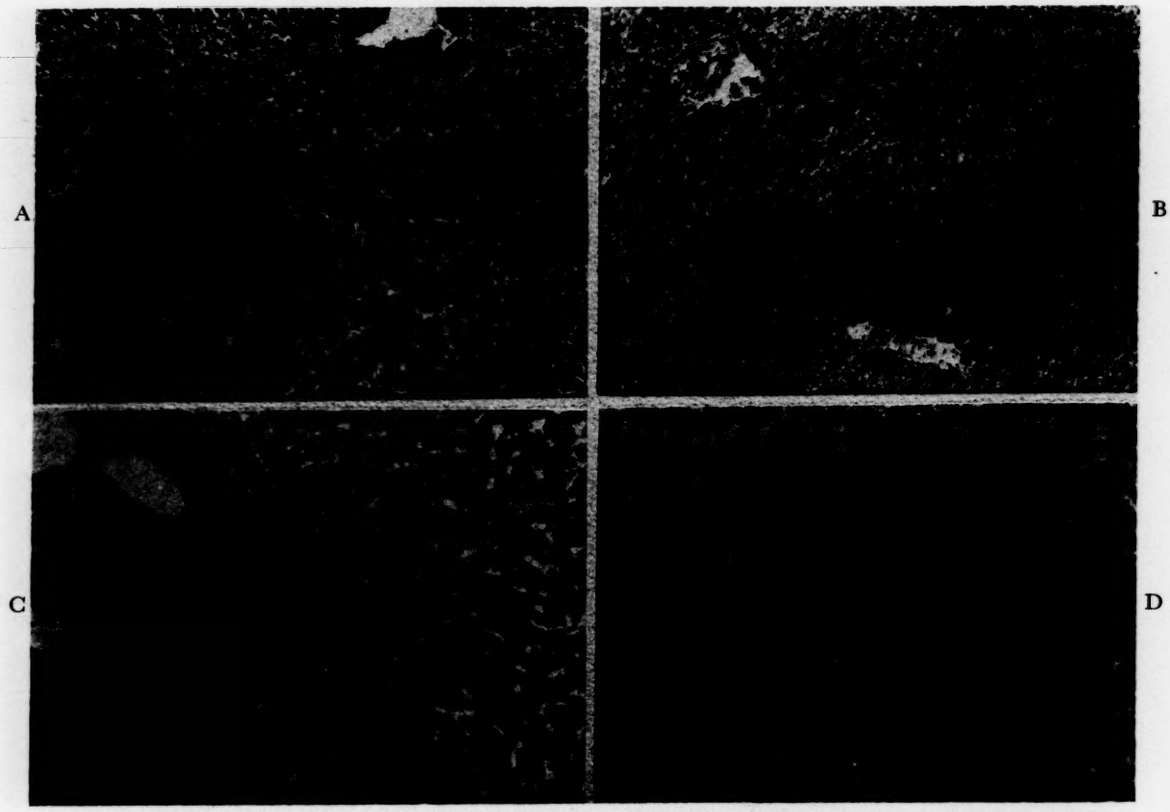


FIG. 6. A, massive necrosis in fulminant viral hepatitis; almost all liver cells have disappeared and are replaced by scavenger cells phagocytosing their remnants; some cholangiolar proliferations are seen (× 80). B, submassive necrosis in toxic hepatitis; some remnants of the lobules are seen around portal triads (× 65). C, periportal necrosis in subacute cholangiolitis; replacement of peripheral zone of lobule by exudate and proliferated cholangioles (× 110). D, pressure atrophy of liver cell plates due to amyloid (× 90).

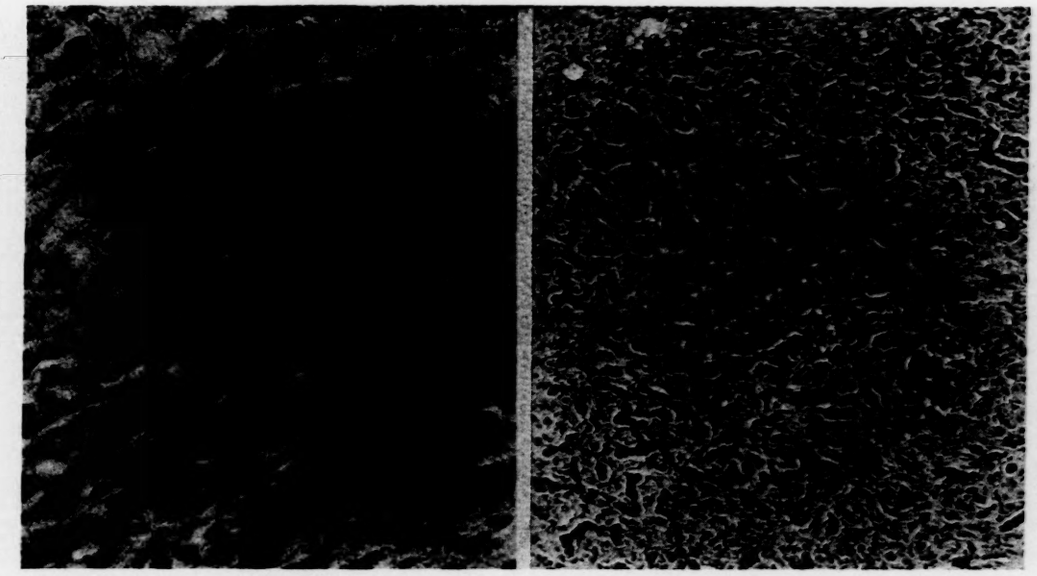
with complete anoxia, which may occur near traumatized surfaces, after ligation of the hepatic artery or after involvement of intrahepatic arterial branches as in periarteritis nodosa. It is possible that in these instances the portal vein blood flow also is locally compromised.

Periportal necrosis (Fig. 3C) is the result either of interference with the blood flow on the periphery of the lobules by fibrin thrombi as in eclampsia[62] or, far more important, is associated with and possibly caused by inflammation on the periphery of the lobule and in the portal triads. This will be discussed in greater detail in the section on mesenchymal reaction. (Fig. 6C.)

Regeneration. The liver is capable of rapid and extensive regeneration and can rapidly replace extirpated portions.[32] This regeneration may be a marginal process near the site of the lost liver tissue either within the liver cell plate (physiologic wear-and-tear, exaggerated after focal or spotty necrosis) or on the border of areas of central or submassive necrosis. Cells grow into the parenchymal spaces denuded by the necrosis and expand them if they have collapsed.

Signs of regeneration are cytologic (dark cytoplasm, multinucleated cells and giant cells) (Fig. 7A) or characterized by formation of plates two or more cells thick, as in the embryonal state.[12] In addition, the loss of liver tissue causes some regeneration in remote parts of the liver as demonstrated in parabiotic rats after removal of a large part of the liver of one parabion.[63] Ductular proliferation, often called bile duct proliferates, is probably also an expression of regeneration of liver cells, in view of recent embryologic experiences,[13,15] despite some of the older interpretations.[64] (Fig. 7B.) Intralobular regeneration produces a very bizarre picture and the functional capacity of these unusual configurations cannot be evaluated from the biopsy specimen.

Fatty Metamorphosis. Increase of the fat content of the liver cells may be reflected in the



A B

FIG. 7. Forms of regeneration. A, giant cell formation in subacute viral hepatitis; cellular exudate surrounding degenerating and regenerating liver cell plates (× 290). B, proliferation of cholangioles around liver cell remnants in diffuse septal (alcoholic) cirrhosis (× 75).

presence of smaller or larger intracytoplasmic droplets. In contradiction to older concepts, the size of the droplets is not functionally important. The escape of fat from liver cells to form fatty cysts has recently been described. (Fig. 8A.) This results in an "extracellular" deposition of fat which is re-absorbed only with difficulty into the liver cells and is usually removed via blood and bile channels.[65] Fatty metamorphosis usually starts in the center; however, the significance of the lobular distribution is still not fully understood. Fatty liver, resulting from increased accumulation or formation of fat or reduced removal and oxidation, occurs in (1) toxic injury (carbon tetrachloride, chloroform, phosphorus[66]); (2) hypoxia[52] ("hypoxemic fatty degeneration"[67]); (3) hormonal imbalance (pituitary hormones increase the transport of fat from the periphery, and fatty metamorphosis is found in insulin deficiency[68] and obesity[69]); (4) nutritional deficiency (most emphasized in the past decades), especially lack of methionine and choline (fatty liver in alcoholism[70] or malignant malnutrition of kwashiorkor[71,72]). These and other related substances have been considered lipotropes, responsible for the normal removal of fat from the liver and serving in the formation of phospholipids which act as carriers of fatty acids[73] or assisting in the oxidation of fatty acids. The ready removal of fat by proper diets and even by bedrest alone has been demonstrated by serial liver biopsies;[74] however, some fat deposition resists therapy for prolonged periods, for reasons that are still poorly understood.[75] Although histologically a very impressive phenomenon, fatty metamorphosis is functionally of surprisingly little significance as far as most hepatic tests are concerned.[36] If severe fatty metamorphosis is produced in experimental animals by the methionine antagonist, ethionine,[76] or by a choline-deficient diet,[77] the only hepatic test which gives abnormal results is the measurement of bromsulfalein extraction. This may be an expression of impaired lobular circulation due to the swelling of liver cells.[18] If the fatty metamorphosis is associated with liver cell damage, as in protein deficiency, functional impairment is present which is not altered by removal of the fat.[77] In clinical uncomplicated fatty metamorphosis, functional liver damage is not a necessary accompaniment.[70] This does not mean that fat in the liver is innocuous. Patients with large fatty livers due to nutritional deficiencies (alcoholism) without cirrhosis may suddenly develop severe, often fatal, hepatic failure with jaundice. The focal necroses in the liver found at autopsy suggest increased vulnerability of the fatty liver to toxic substances.[78] (Figs. 8B and C.) This is supported by the observation that upper respiratory infections often usher in the dramatic terminal episode. Moreover, the

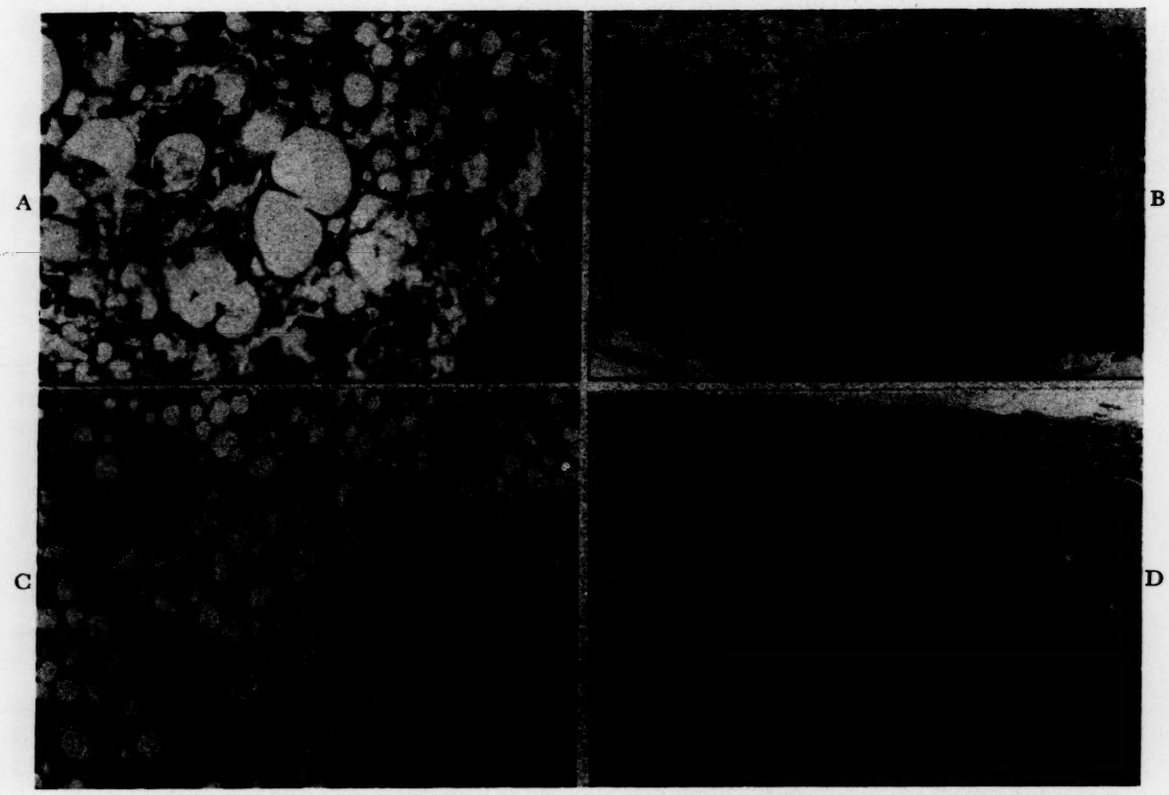


FIG. 8. A, fatty cysts due to merging of large liver cell drops of two cells in alcoholic fatty liver (× 230). B, alcoholic fatty liver with severe jaundice revealing focal and periportal necrosis. C, strands of segmented leukocytes extending into the parenchyma particularly around necrotic liver cells in alcoholic fatty liver with jaundice (× 160). D, primary intrahepatic cholestasis (acute "cholangiolitis") of suggested viral etiology; central bile stasis; otherwise no liver cell degeneration and normal portal triad (× 60).

presence of fat favors the development of cirrhosis, directly or indirectly.

Cholestasis. Cholestasis is the result of extrahepatic biliary obstruction due to stones, tumors and scars or may be due to intrahepatic processes. Stagnation of bile flow produces pigmentation of cytoplasmic components of Kupffer and liver cells and bile plugs in dilated bile capillaries in the center of the lobule. The latter appear on the lobular periphery only in inflammatory lesions. In prolonged cholestasis feathery degeneration, portal circular fibrosis and "bile duct proliferation" develop.[79] Cholestasis is associated with hyperbilirubinemia and bilirubinuria and with a rise in serum alkaline phosphatase (supposedly related to proliferating cholangioles[80]), and in serum cholesterol and serum phospholipids. The mechanism of these elevations is not fully understood. It is not only a retention of substances excreted in the bile but also a reflection of altered metabolic function. The lipid elevation may be out of proportion to the other changes for unknown reasons. In prolonged intrahepatic cholestasis particularly, the serum cholesterol elevation may become so great as to produce skin xanthomatosis.[81] The so-called xanthomatous biliary cirrhosis, seen chiefly in women, is morphologically a chronic pericholangiolitis.[82] Intrahepatic cholestasis may be associated with inflammatory changes in the border area between portal triads and lobular parenchyma and with proliferation of peripheral and occasionally intralobular cholangioles. Acute or chronic inflammatory exudate may surround the cholangioles or appear within their lumen. This histologic picture of intrahepatic cholestasis associated with functional evidence of cholestasis may complicate various diseases associated with liver cell degeneration. Sometimes it occurs without morphologic or functional evidence of liver cell degeneration as in some instances of intoxication with arsenicals[83] and of hematogenous bacterial infection.[84] It is possible that occasionally this may be also a manifestation of viral

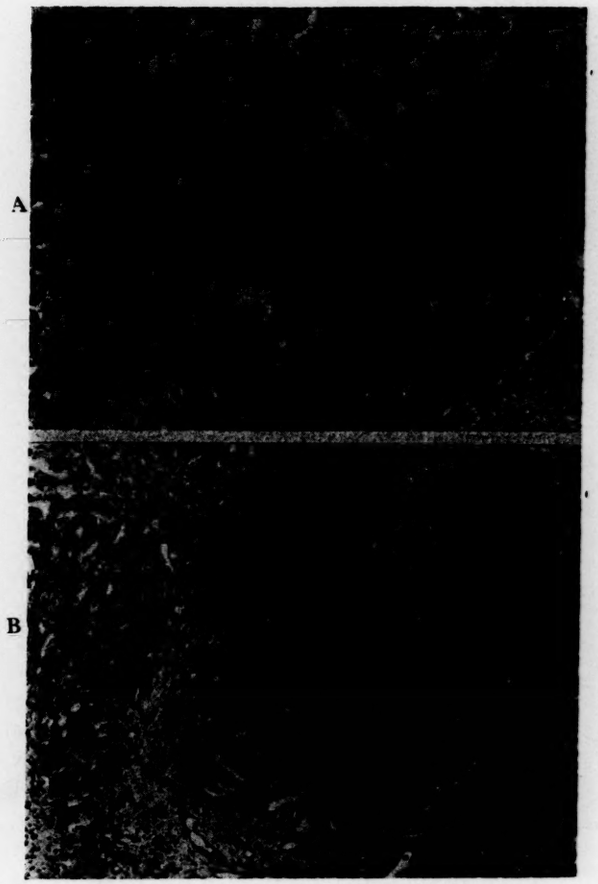


FIG. 9. Extrahepatic biliary obstruction of over four weeks' duration in carcinoma of pancreas. A, microcalculi in dilated bile ducts in portal triad (× 90). B, bile extravasate from dilated bile duct in portal triad; destruction of biliary epithelium; granulation tissue surrounds the gold-brown extravasate (× 102).

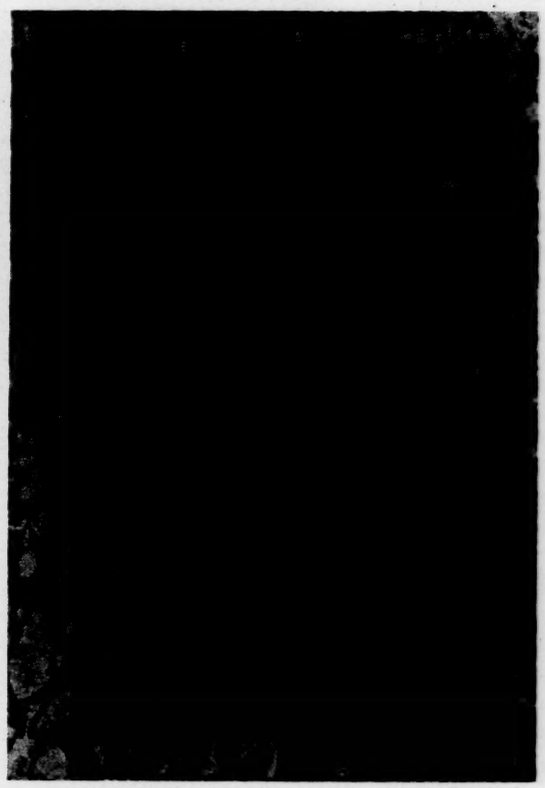
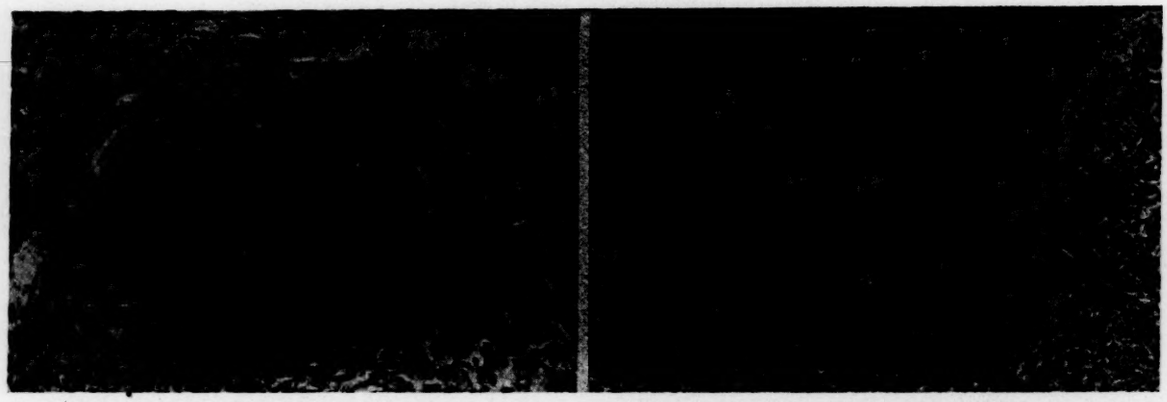


FIG. 9C. Bile infarct near portal triad; reticular appearance of bile pigmented necrobiotic liver cells after loss of most cytoplasm (× 115).

hepatitis. (Fig. 8D.) This lesion has been considered to be the result of an abnormal permeability of the ductules for bile due to inflammation, with subsequent regurgitation into the blood, and the term cholangiolitis has been proposed.[85] However, it may represent a primary intrahepatic disturbance of the bile flow with resulting escape of bile and secondary irritation and inflammation. The difficulty in understanding this lesion lies in the circumstance that in acute intrahepatic cholestasis the morphologic signs are neither conspicuous nor characteristic. Intrahepatic disturbance of bile flow occurs, for instance, in methyl testosterone poisoning[86] without any evidence of inflammatory exudate. Only if intrahepatic cholestasis is protracted does the morphologic picture become almost diagnostic.[81,87,88] (Fig. 6C.) The absence of morphologic criteria of acute "cholangiolitis," "pericholangiolitis" or intrahepatic cholestasis renders the differential diagnosis between intrahepatic (medical) jaundice and extrahepatic (surgical) jaundice in biopsy specimens difficult. Since clinical and laboratory methods also often fail, any help available from liver biopsy is important. While in earlier stages the histologic differential diagnosis is almost impossible, later on characteristic lesions may appear in extrahepatic obstruction, which involves the entire intrahepatic biliary tree and not only the ductules and parenchyma as in the intrahepatic form. Therefore, only in extrahepatic obstruction does one find (1) microcalculi of inspissated bile in the intralobular bile ducts in the portal triads (Fig. 9A); (2) extravasation of bile with granuloma formation in the portal triads (Fig. 9B); and (3) focal peripheral necrosis with rarefaction of pigmented liver cell cytoplasm (Fig. 9C) (bile infarcts[89] explained by focal interference of the circulation due to dilated bile ducts). The presence of any of these changes is diagnostic of an extrahepatic obstruction but



A B

FIG. 10. A, extensive infiltration of portal triads with round cells, some pigment-containing, in viral hepatitis; irregular proliferation of cholangioles; liver cell degeneration (× 160). B, portal inflammation with periportal necrosis and perilobular extensive fibrosis in chronic cholangitis due to biliary stricture; lobular architecture is intact (× 39).

their absence does not exclude it and surgical exploration may, under such circumstances, be the final recourse. If the extrahepatic bile ducts are narrow, the jaundice is due to an intrahepatic process and further surgery is unnecessary. The only exception is a carcinoma at the bifurcation of the common hepatic duct in the liver which is also not amenable to surgery.

Mesenchymal Reaction (*Inflammation*). This process may involve the intralobular parenchyma or the portal triads. Kupffer cell mobilization occurs either as part of a systemic response, e.g., in subacute bacterial endocarditis, or as a reaction to liver cell injury and is therefore common to many liver diseases. The cytoplasm of the swollen Kupffer cells is very basophilic, suggesting increased protein formation, presumably serum gamma globulin.[90] Focally excessive proliferation of Kupffer cells associated with infiltration and proliferation of wandering inflammatory cells causes granulomatous nodules of greater or lesser size. They may become diagnostic in such diseases as tuberculosis, Boeck's sarcoid, brucellosis, histoplasmosis and Hodgkin's disease. Local obstruction of the sinusoids by such Kupffer cell granulomas may lead to focal necrosis, e.g., in typhoid fever.[54] Acute or chronic inflammatory cells may accumulate in the portal triads, sometimes around the lymphatics. This is often associated with proliferation of local mesenchymal cells containing pigment. Such inflammatory lesions are frequently found in infections of all types including systemic infections, viral hepatitis, and gallbladder and gastrointestinal disorders.[91,92] (Fig. 10A.) They represent a response to toxic substances reaching the liver either from the gastrointestinal tract or through the systemic circulation and in the vast majority of cases they are not related to the relatively rare ascending infection in the bile ducts. It is possible that this inflammation results from toxic material which has passed through the sinusoidal walls and is being drained through the tissue spaces to the lymphatics in the portal triads. It is the most frequent histologic alteration of the liver and is found in almost every adult liver in at least some portal triads.[8] These inflammatory cells may exhibit basophilic cytoplasm and they, together with the proliferated Kupffer cells, are possibly responsible for the elevated serum gamma globulin levels commonly encountered in liver diseases.[8,40] However, there is little correlation between milder degrees of portal inflammation and functional changes. More severe types of morphologically similar inflammation occur in viral hepatitis, cirrhosis and in primary intrahepatic cholestasis (cholangiolitis). (Fig. 6C.) This applies also to extrahepatic biliary obstruction with superimposed infection (more often hematogenous than ascending) in which the inflammatory response may become especially severe, even producing abscesses. Involvement of small interlobular or septal bile ducts and ductules is probably secondary. If this portal inflammation is severe, it spreads into the periphery of the lobules in the form of streaks composed of inflammatory cells, including segmented leukocytes. The limiting plate becomes disrupted, the periportal liver cells necrotic and the

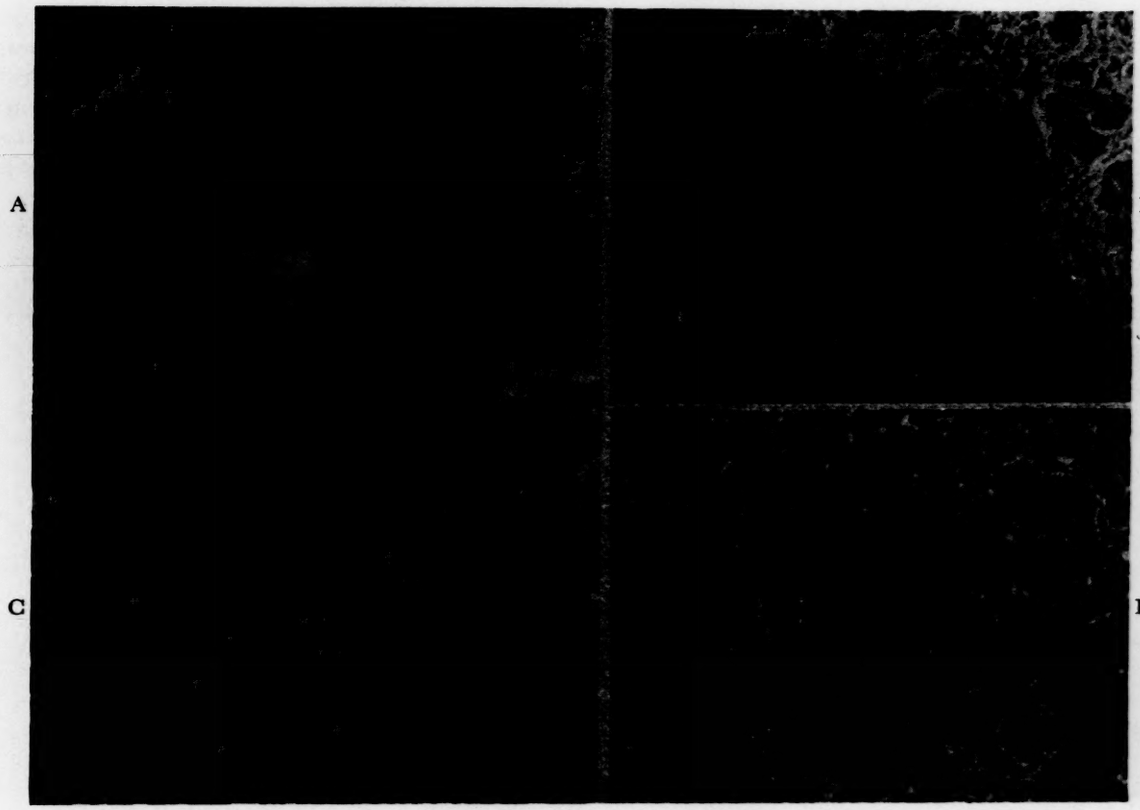


FIG. 11. A, massive collapse after viral hepatitis; portal and central fields are approximated; their structure differs from the collapsed framework (× 60). B, submassive collapse after hepatitis of unknown etiology (× 80). C, straight septum (probably developing in plane of stress) originating in portal triad and dividing lobule of fatty liver (× 120). D, aggregated follicles, some of them containing giant cells near portal triad in Boeck sarcoid of liver (× 55).

border between parenchyma and portal triads unclear. The simultaneous proliferation of ductules is probably a response to their severance from the bile capillaries.[30] In this periportal zone of inflammation and hepatic necrosis the framework collapses and new formation of fibers ensues, with enlargement of the portal triads. (Fig. 10B.) Fibrosis and inflammatory exudate prevent regeneration of liver cells and the portal triads remain enlarged even after subsidence of the inflammatory process. A new limiting plate is formed at the periphery of the remaining lobule.[93] Perilobular fibrosis as an end-result of various inflammatory lesions may regress, as has been shown in viral hepatitis.[94]

Cirrhosis. Cirrhosis is a chronic hepatitis with abnormalities of both parenchyma and mesenchyma, including scarring. Its definition is much debated[27,45,95] and some consider the mesenchymal changes[27] and others the parenchymal ones the primary lesion.[96] From a functional standpoint cirrhosis has to be considered as an altered reconstruction of the lobular parenchyma due to injury of various etiology and developing along definite pathways. Of all the morphologic features, it is the degree of histologic liver cell damage which is best correlated with clinical or biochemical activity, and best indicated by abnormal cephalin flocculation and thymol turbidity tests. Some of the inflammatory features correlate with the serum protein reactions. The scarring, however, is related only to the development of ascites and the serum albumin level, not to the results of any of the hepatic tests.[97] There are several pathways to cirrhosis formation.[98]

Postcollapse changes: (Fig. 4.) Massive necrosis of whole lobules causes complete collapse of the reticulum framework with approximation of portal and central canals after the disappearance of the liver tissue. (Fig. 11A.) In the surrounding intact liver parenchyma, planes of stress develop along which liver cells disappear and are replaced by connective tissue membranes which

transform the planes of stress into septa dissecting the lobules.[98] The more common submassive necrosis results in a partial collapse of the lobule (Fig. 11B); the residual irregular fragments may represent small parts of a lobule or larger continuous garland-shaped confluent fragments of neighboring lobules or larger pieces originally belonging to several lobules in which the portal vein and sometimes even the central vein is still preserved.[99] The persisting liver tissue regenerates very rapidly both on the edges of necrotic areas and diffusely, apparently due to humoral stimulation caused by the loss of liver tissue. The fragments form round and irregular nodules in which the liver cell plates re-arrange themselves in response to the altered blood flow and pressure relationships. Some of the nodules may be large and may be composed of several original lobules. Characteristically, the nodules vary greatly in size in this type of cirrhosis and even more so from liver to liver. There are extremes ranging from just a few scars separating large nodules (Marchand's nodular hyperplasia) to a very fine granular form.[100–102]

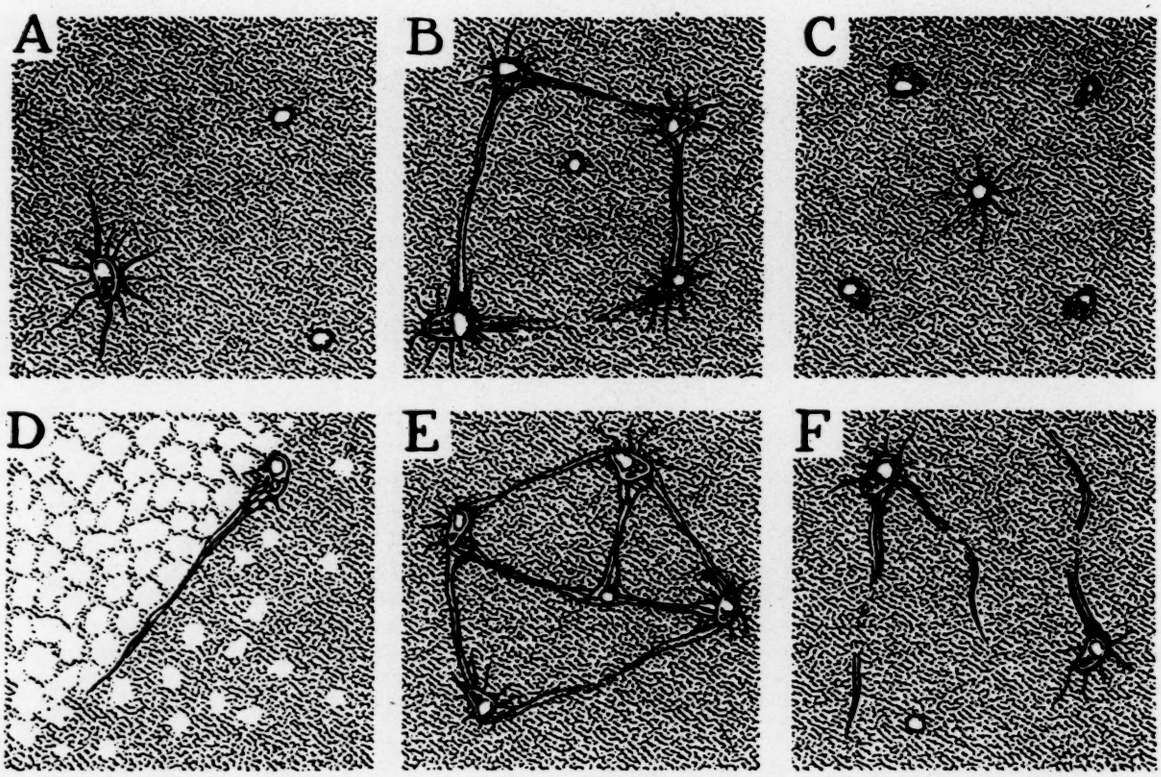


FIG. 12. Diagram of types of hepatic connective tissue proliferation (drawn by Hans Elias). A, periportal fibrosis; B, perilobular fibrosis; C, centrolobular fibrosis; D, septum in fatty liver due to uneven expansion and regeneration; E, nodule formation by septa; F, trabecular pseudocirrhosis.

Portal irritation: Various inflammatory irritations, for instance due to granulomatous diseases, parasites, iron deposition and possibly viral hepatitis, may induce collagenous membrane to develop in the reticulum fiber network radiating from the portal triads. (Fig. 12A.) Liver cells disappear between such membranes, which thus become condensed into septa, dissecting the lobular parenchyma into nodules. Due to altered circulation, the liver cell plates are re-arranged and the nodules start regenerating until the entire lobular pattern is destroyed. (Fig. 12E.)

Central irritation: Prolonged severe right heart failure[103] or repeated insults by toxic substances[49,18] may produce similar membranes radiating from the lobular center. (Fig. 12C.)

Fatty metamorphosis: It is not established whether fatty metamorphosis itself or other accompanying changes produce cirrhosis. However, there is no doubt that prolonged experimental or clinical fatty metamorphosis eventually is followed by cirrhosis.[104,105] Several pathways are possible: (1) Fatty cysts may collapse and their connective tissue capsules serve

as a basis for dissecting septa.[65] (2) Inflammatory lesions around the portal triads or within the lobular parenchyma possibly subsequent to necrosis of the liver cells cause formation of collagenous membranes eventually condensing to septa. The frequent presence of small focal necroses in the periphery of the lobular parenchyma in cirrhosis[106] would support such an etiology. (3) Alternation of areas of fatty metamorphosis and regeneration (plates two-cells thick) in various parts of the lobule due to periodic disappearance of the fat (as occurs in human malnutrition) causes liver plates to rearrange themselves along planes of stress between different portions of the lobules. In these planes liver cells disappear and connective tissue septa form and dissect the lobules. This is probably the most important factor. (Figs. 11C, 12D.)

Chronic pericholangiolitis: Fibrosis developing around ductular proliferations produces connective tissue strands traversing the lobule. (Fig. 12F.) Despite the increase in connective tissue the lobular pattern is not actually destroyed (Hanot's cirrhosis). Septa between these strands develop in late stages; they result in dissection of the lobules with its functional consequences.

Two processes are common to all types of cirrhosis. One is the formation of nodules in which the normal arrangement of branches of the portal and hepatic vein, and therefore the blood flow, is altered and the liver cell plates are re-arranged. Nodules may also exhibit an expanding regeneration of tissue elements which compresses the surrounding tissue, particularly the hepatic vein tributaries and the reticulum framework.[107,108] This venous compression by the nodules is the main cause of portal hypertension in cirrhosis, which is thus related to the degree of nodularity and the size of the nodules.[102,107] The second process is the development of abnormal communications between the portal vein branches and the hepatic vein tributaries. In massive or sub-massive collapse some sinusoids persist, shunting blood directly from the portal to the hepatic vein branches and eventually acquiring a venous lining. Similarly, in the septa already described venous vessels are found acting similarly as venous shunts. They have been considered to result from active angiogenesis[109] but more probably they develop by inclusion of sinusoids during the formation of the septa.[108] These portohepatic venous anastomoses in which the branches of the hepatic artery also participate have been demonstrated by various injection technics.[110,108] They shunt blood past the lobular and nodular parenchyma, which is thus placed at a circulatory disadvantage. They produce the necroses in the center of lobules and nodules which histologically have the character of hypoxic necroses and therefore seem to be the factor which maintains the cirrhotic process even if the original cause (such as virus infection or deposition of fat) has disappeared. The functional significance of these shunts decreases if the normal plate architecture is restored. In principle, the portohepatic anastomoses, together with the regenerative nodules, characterize cirrhosis.

In summary, several main morphogenetic types of hepatic fibrosis exist in which some specific features may point to the etiology: (1) *Postcollapse cirrhosis* (*synonyms:* postnecrotic cirrhosis;[95] toxic cirrhosis;[45] coarse nodular cirrhosis or multiple nodular hyperplasia;[111] postnecrotic scarring;[18] multilobular cirrhosis; chronic liver atrophy) which is primarily the result of preceding viral infection in this country but which could result from toxic or nutritional (tropical)[71] injury. (2) *Diffuse septal cirrhosis* (*synonyms:* portal cirrhosis, Laennec's cirrhosis [of the American literature—the German literature designates as Laennec's any atrophic cirrhosis], diffuse or granular or unilobular cirrhosis or diffuse hepatic fibrosis[18]) which is caused predominantly by malnutrition (including alcoholism or other causes of fatty metamorphosis). But the same picture may eventually result from hemochromatosis, parasitic infestations, late stages of intrahepatic or extrahepatic cholestasis especially if associated with bacterial infection, prolonged and severe cardiac insufficiency (as in constricting pericarditis or exceptionally in tricuspid incompetence[103]), and possibly also from chronic granulomatous or viral hepatitis. (3) *Trabecular pseudocirrhosis* (Fig. 12F) which develops from extrahepatic or intrahepatic cholestasis before significant septa formation has taken place. (4) *Portal fibrosis* (Fig. 12A) including perilobular fibrosis (Fig. 12B) as the result of periportal inflammation. (5) *Central fibrosis* (Fig. 12C) primarily due to passive congestion (congestive pseudocirrhosis[103]).

Only the first two groups fulfill the criteria of cirrhosis and transitional forms between them occur. Septa formation may complicate postcollapse cirrhosis while collapse may be found

in septal cirrhosis after massive necrosis of lobular and also reconstructed nodular parenchyma. All types of cirrhosis thus may have a common terminal pathway for which possibly the name Laennec's cirrhosis could be reserved in analogy to the use of the term Bright's disease for a similar stage in renal diseases.

CONCLUDING REMARKS ON LIVER DISEASES

Some fragmentary remarks may serve as an introduction to the following parts of this symposium. Almost all clinical disorders reveal some of the listed structural phenomena in varying degrees. Among the *diffuse hepatic disorders* the lesion most commonly seen in liver biopsy specimens is *non-specific reactive hepatitis* which is characterized by a mild degree of liver cell damage, focal necroses of various size, Kupffer cell mobilization and inflammation in the portal triads. This lesion, to which many names have been given, such as infiltrative hepatitis,[112] is found in a large variety of disorders including infectious diseases (e.g., malaria[113] or pneumonia), gastrointestinal disorders (ulcerative colitis,[114] gallbladder disease[115] and peptic ulcer.[112,116]) It probably results from injurious material reaching the liver via the portal vein. Some features of the lesion are found in biopsy specimens obtained after long abdominal operations;[117] this reduces the value of surgical biopsies. The non-specific nature of the lesion prevents recognition of the etiologic factors. The liver cell damage is generally mild or present only focally, which explains the poor correlation between the histologic findings and the erratic results of the hepatic function tests,[112,118] including the serum protein reactions, due mainly to elevated serum gamma globulin; these apparently reflect concomitant mesenchymal irritation in or outside the liver rather than hepatocellular injury. Non-specific reactive hepatitis probably is the morphologic basis of the abnormalities in some of the hepatic tests reported in many non-hepatic diseases which are not associated with circulatory disturbances. Knowledge of the histologic picture of this condition is important in the diagnostic interpretation of liver biopsy.

Viral hepatitis is clinically probably the most significant hepatic disorder. In its most common form, the benign and self-limited type of acute viral hepatitis, a "spotty" necrosis is associated with intralobular and peripheral mesenchymal reaction. Especially in the early and defervescent stages the mesenchymal reaction predominates so that some consider the disease a primary reticuloendothelial disorder with secondary hepatic involvement.[119] Nevertheless, it appears that either both parenchyma or mesenchyma are simultaneously attacked by the virus or that the mesenchymal change is only a response to parenchymal injury.[41,53,120] Functionally, the diffuse hepatocellular damage accompanying the necrosis is in the foreground, at least in typical cases. The characteristic single cell necrosis with formation of acidophilic bodies most probably results from different speeds of virus growth in different cells in the same lobule. Other degenerative changes such as the swollen "balloon cells" are possibly due to focal anoxia caused by exudate disturbing the lobular circulation. Exceptionally, in the most severe cases, a circulatory lesion progresses to central necrosis[41,121] which therefore is not seen in the usual biopsy specimens. In some instances all liver cells of a lobule simultaneously become necrotic. The extent of this massive necrosis determines the clinical course which may vary from simultaneous involvement of the entire liver, fulminant hepatitis,[61] to gradual involvement of lobule after lobule in the chronic disorder noted in epidemic form in the Scandinavian countries (malignant hepatitis).[122] While none of the different individual features of viral hepatitis are specific (such as acidophilic bodies, accumulation of round cells around necrotic liver cells and round cell portal infiltration), their occurrence in combination permits a diagnosis in biopsy specimens in many cases.[26,42,120,123] The most diagnostic feature, however, is the great variation of alterations from cell to cell but this is seen also in the hepatitis of infectious mononucleosis.[124] Gross polymorphism characterizes the fatal form which usually exhibits predominant involvement of the left lobe. The protracted stages of hepatitis present a greater problem morphologically.[125] In the relatively rare instances in which marked liver cell damage persists the findings are those either of prolonged "spotty" necrosis or of recurrent massive necrosis and collapse ending in postcollapse cirrhosis.[102,126] The highest serum gamma globulin elevations observed in liver disease are found in this type of cirrhosis,[127] in addition to signs of cholestasis and liver cell degeneration. In some rare instances ductular involvement with the clinical picture of chronic intrahepatic cholestasis ("cholangiolitis") dominates the picture.[85]

The most common protracted form has in addition to scattered single cell necroses, often overshadowed by focal intralobular regeneration, a persistent mesenchymal reaction. This may take the form of intralobular nodules ("Spaetknoetchen"[53,128]) with portal inflammation often associated with elevated serum gamma globulin. This may be followed by perilobular fibrosis which subsequently disappears.[94] A non-specific stage develops which fades into the non-specific reactive hepatitis. The lack of correlation of the anatomic findings with functional changes is most disturbing in this stage[94,125] as is the poor correlation of both with clinical manifestations, which are predominantly gastrointestinal and neurasthenic.

In *toxic hepatitis* the morphologic manifestations are often not clearly separated from congestive and anoxic changes, possibly because such factors as swelling of the liver cells in the periphery of the lobule[18] or contraction of the hepatic veins[55,57] often complicate the cytotoxic disturbance of cellular respiration. The lesion thus largely depends upon blood flow and is chiefly a central necrosis sometimes with fatty changes (as in carbon tetrachloride[129] or mushroom poisoning[130]), in contrast to the more spotty alterations of viral infections. The inflammatory reaction is usually subdued, possibly due to hypoxic inhibition of the inflammatory cells, and a silent denudation of the framework results.[131]

Nutritional hepatic injury produces a variety of morphologic alterations. Starvation (in man) results in atrophy of the liver cells with wear-and-tear pigment deposition.[132] Deficiency of sulfamino acids associated with deficiency in alpha-tocopherol produces massive necrosis in experimental animals.[133–135] However, it is not established to date whether or not a counterpart to this exists in man, at least in the temperate zone. The lesion most commonly seen there results from imbalanced nutrition; specifically, relative deficiency of protein and excess of carbohydrates and fats. This is the fatty liver seen in alcoholics which is followed by a diffuse septal cirrhosis.

The morphologic changes of *focal hepatic disorders* have been diagnosed in recent years with increasing frequency by liver biopsy, which has thus opened up a new diagnostic approach to diseases not primarily hepatic. In addition to the demonstration of lymphomas and secondary carcinomas,[136] the differential diagnosis of the granulomas has been developed. This includes brucellosis,[137] histoplasmosis and especially Boeck's sarcoid[138–140] (Fig. 11D) and tuberculosis.[141,142] Elucidation of the etiology of the hepatic granulomas is improving with increasing experience and otherwise unsuspected instances of miliary tuberculosis have been detected.

SUMMARY

Recent developments in the morphology of hepatic disorders are reviewed in the attempt to coordinate them with each other and to correlate them with functional changes. The widespread use of liver biopsy has greatly facilitated this approach. In normal anatomy new structural concepts of the parenchyma and vascular distribution have been developed to a great extent on the basis of newer technics including three-dimensional analysis. The poor correlation between observations in biopsy and necropsy specimens is discussed. The difficulties in the general correlation of the histologic picture in liver biopsy specimens with clinical manifestations and laboratory findings is pointed out. Nevertheless, some correlation can be developed with individual component lesions which, together, produce the morphologic picture of liver disease. The appearance, morphogenesis, differential diagnosis, etiologic factors and functional correlations of the various forms of the following lesions are discussed: liver cell degeneration; hepatocellular necrosis; fatty metamorphosis; cholestasis; mesenchymal reaction (inflammation); and cirrhosis. This is followed by concluding remarks on clinical liver diseases (including the diffuse and focal varieties). The hope can be expressed that wider experience with the morphologic changes of the liver during life may eventually better consolidate not only the histologic differential diagnosis but also the coordinated classification of hepatic disorders.

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Conference on Therapy

Most Effective Application of Therapeutic Measures in the Management of Congestive Failure

These are stenographic reports, which have been edited, of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

Dr. Harry Gold: The treatment of the heart diseases has advanced along several fronts in recent years. Surgical transformations in congenital heart disease and surgical repair of acquired heart disease have provided many dramatic developments. They have attracted the most attention in reviews of progress and have tended somewhat to eclipse the general interest in an area of progress which may in a sense be considered more important because the developments here involve the lives of much greater numbers. I refer to the advances which have taken place in the management of congestive failure, a disturbance of the heart and circulation which causes serious disability in about 30 per cent of the cardiac population. The evolution here has been more gradual but no less substantial. The patient with suffocation at rest, shortness of breath on the slightest exertion, massive swelling of the legs and such other symptoms as are commonly associated with advanced congestive failure used to dominate the scene in the doctor's office, and the medical and cardiac clinics. They are still there but their numbers are rapidly dwindling. What has brought this change about is the subject of the conference today. Dr. Hugh Luckey will tell us something about it.

Dr. Hugh Luckey: I should like first to define the condition. At first sight it would seem a simple matter to define congestive heart failure. In actual fact it is very difficult to find a definition which is not an oversimplification and does not leave important segments out of consideration. The best I can do is to say that congestive heart failure is the result of a primary failure of the heart to maintain the proper blood flow and pressure relationships in the vascular system, and this brings about a disturbance in volume and distribution of blood with increase in the volume of extracellular fluid. The primary defect, therefore, is impaired cardiac function. The ultimate result is disturbed renal function with salt and water retention. It is the latter which accounts for many of the subjective and objective features of congestive failure. The edema is one of the important factors in the respiratory difficulty. Congestion of the liver is the most prominent cause of abdominal discomfort. An increase of the inflow load to the heart incident to the large blood volume completes the vicious cycle.

The measures that are used for the most effective management of this state fall into two groups: (1) those directed toward the heart, the primary site of the difficulty, and (2) those directed toward the secondary factor, the edema.

Any orderly approach to the management of congestive failure requires consideration of the fact that most of these patients present an immediate precipitating factor of some type. It may be an infection of a general nature or a specific infection of the heart itself. It may be some unusual physical or mental exertion or some metabolic disturbance such as hyperthyroidism which brings about an unusual demand for cardiac work. The discovery of the precipitating factor in a particular case is manifestly desirable to insure the best treatment.

In the direct approach, physical rest is a factor

of first importance. This may mean rest in bed although the bed is not always desirable. The patient should be in that position in which he obtains optimum rest. Sitting in a comfortable chair is sometimes preferable to bed rest.

Digitalis still remains the most useful agent for the purpose of securing maximum cardiac function. The selection of a member of the digitalis group and its proper administration is the most vital measure in the treatment of the patient with congestive failure.

There are special varieties of congestive failure, such as acute pulmonary edema, which require special consideration but which I believe we do not have sufficient time to go into at this time. I should like to direct my remarks chiefly to the manner of treating the more usual type of patient with congestive failure. This might be represented by a fifty year old man with a long-standing history of hypertension, with recent symptoms suggesting coronary insufficiency. During recent months he has noted a decreasing capacity for exertion and now, in association with a mild respiratory infection, he develops severe dyspnea, orthopnea, swelling of the ankles and such other features as are commonly related to the state of congestive failure. The cardiac rhythm may be normal.

While it is possible to carry out the regimen of treatment in the home, it is usually preferable to initiate treatment with the patient under observation in the hospital. With bed rest alone and elimination of precipitating factors such as infection, a proportion of these patients have diuresis and recover from the congestive failure. In others, however, the failure persists and is brought under control only after various measures are applied. I have already mentioned the matter of digitalization. Sodium restriction is another measure of much importance. The patient with heart failure has an altered capacity to handle sodium. The ordinary ward diet contains an amount of sodium corresponding to from 3 to 6 gm. of sodium chloride. The average patient with congestive failure tends to retain some sodium on such a diet. It is therefore necessary to restrict sodium. The dietary intake of sodium chloride can be reduced to about 1.5 gm. with foods that are commonly available in most hospitals, by a relatively simple system of selection. The object is to allow an adequate caloric intake in a diet as palatable as possible in order to avoid adding to the patient's total discomforts. We do not consider it necessary to put in effect extreme restrictions in sodium as are sometimes recommended since we find that it is unnecessary in the average patient with heart failure. When more extreme sodium restriction is necessary, restriction to a sodium intake of only 2 to 7 mEq., we have usually found it convenient to change to the rice diet since this diet is a fairly standard item in hospitals.

We do not look upon milk as a satisfactory initial diet in these cases. Most adults are relatively intolerant of milk. These patients will often present as their primary complaint the fact that all they have in their diet is milk. They would like to have more food to eat. There is also the fact that milk is not a low-salt food when compared with other low-salt foods. The intake of salt is low on a milk diet because the calories are so restricted. If one were to give a milk diet representing the basal caloric requirement of 25 calories per kg. of body weight, the patient would be receiving from 2.5 to 3 gm. of sodium chloride.

There seems to be a controversy about water restriction but I think it is not justified. Views concerning water intake have advocates at both extremes. There are those who have urged marked water restriction and those who have recommended huge amounts of water, 6 to 7 L. a day, as in the Schemm regimen. It seems to me that the results have not been materially different, and it is likely that when such opposite practices yield the same results the consideration of water does not have the importance that is assigned to it. Retention of water in the patient with heart failure is not a primary difficulty. Retention of sodium is primary. The patient with heart failure often eliminates water quite promptly. It is our view that the patient should be allowed as much water as is indicated by his thirst. We do not attempt to maintain the water intake at a high level. We leave it entirely up to the patient. In the patient with congestive failure there is no evidence that we change the rate of glomerular filtration by the use of large quantities of water and there is indication that in most patients the renal function is adequate to maintain satisfactory urine flow for adequate elimination of metabolites.

This regimen of restricted physical activity, adequate digitalization, moderate restriction of salt and water *ad libitum* will result in sufficient diuresis in a number of patients. I have had some difficulty deciding how large a number. Some

years ago Dr. Henry Christian pointed out that such a plan of treatment did not in his experience result in complete elimination of edema in most patients. That has also been our experience. Because of the fact that recovery has been incomplete and relatively slow another factor has been added to the regimen of treatment. I think this factor is largely responsible for the improved outlook in the management of patients with congestive failure which Dr. Gold mentioned at the beginning. I refer to the use of a potent mercurial diuretic. These agents act on the kidney directly to promote the elimination of salt and water. There has been some question as to how often they should be given. The recommendation for use of the daily dose of the mercurial has stirred up a controversy. About five years ago a study was carried out at the Bellevue Hospital to look into the possible dangers in the daily use of the mercurial. Over fifty patients were given a daily dose and carefully studied with special reference to electrolyte disturbances. There was only one instance with indications that the rapid diuresis might have caused some trouble. I say "might" because even in this case there were other factors which could have been responsible. The results were good. No marked electrolyte imbalance was encountered. Recovery was prompt. This study led us to the conclusion that the use of the daily dose of the mercurial, together with other measures which I have mentioned, is a safe procedure and results in an improvement in the majority of patients with congestive failure.

It is our view, however, that the daily mercurial injection is not necessary in a majority of patients after the first few days. In the study to which I referred we found that as the urine volume decreased and the patient's weight leveled off there was a tendency for some elevation of the blood urea nitrogen and for the appearance of complaints of weakness. It seemed to us that we might have gone past the point of optimum weight and that excessive dehydration might have taken place. We have therefore adopted the plan of giving the mercurial diuretics daily only for the first three or four days, in the initial phase of management, and then of spreading the interval between the injections. This probably prolongs somewhat the total period for recovery but I believe that in this way we are more likely to reach the point of optimum body weight with less chance of going beyond that.

I think one cannot emphasize too strongly the importance of daily weighing of the patient as a measure of the efficacy of treatment in removing edematous fluid. When the body weight begins to increase, this does not necessarily call for an increase in the frequency of the dose of the mercurial but rather for examination of the whole therapeutic regimen. This should include re-evaluation of the diet as well as of the adequacy of the digitalization.

We have had some experience with the resins in the management of these patients. Their only advantage that we are able to see is that of decreasing the frequency of the mercurial diuretics. This does not seem to be much of an advantage since it is so simple to use the mercurial diuretics. Patients can inject preparations subcutaneously themselves at home during the period of maintenace. Furthermore, we have not been impressed with the usefulness of the resins in patients with the refractory form of heart failure.

I should like to spend the last few minutes on the subject of the refractory state of heart failure. Much has been written on the point that electrolyte imbalance often accounts for the refractoriness. This is infrequent. I am inclined to believe that the reverse is more often the case and that electrolyte imbalance is frequently produced in the course of the treatment of refractory heart failure. A case in point is that of the patient in advanced heart failure with anasarca and normal electrolyte concentrations who has been on extreme salt restriction and has become completely unresponsive to the mercurials. Such patients have then been treated with resins, and we have observed that during such treatment hyponatremia was produced with no change in the patient's body weight. Most patients of this type will not have diuresis when the plasma sodium is elevated to normal, although this does in occasional patients return to the responsive state.

We believe that most cases of refractory heart failure will be found to fall into two groups. There is the group in which the heart disease has progressed to a point where cardiac output has fallen so far as to be inadequate to maintain sufficient renal function. This is the terminal phase in the natural history of the heart disease. There is the other group in which one may have failed to recognize associated and complicating factors which may be brought under control. One cannot overemphasize the importance of

thyrotoxicosis in this respect. Constrictive pericarditis is one of the conditions which is often overlooked. Primary hepatic or renal disease not uncommonly complicates the picture. One should of course mention the fact that before the patient is regarded as truly refractory, it is imperative to examine and re-examine the total regimen of treatment to insure that the various measures have been adequately applied.

Finally, a few words about two of the complications that arise in the course of the management of congestive failure, namely, hypochloremic alkalosis and the low-sodium syndrome. In the majority of patients with heart failure who develop diuresis from any cause, the amount of chloride which appears in the urine is high in relation to the sodium loss. This produces hypochloremic alkalosis which is usually of moderate degree and inconsequential but may be exaggerated in patients who lose huge volumes of fluid, whether this takes place during the use of the mercurial or in association with any other measures. This phenomenon has been observed in patients who showed marked diuresis with digitalis and bed rest alone. We have observed it in one patient whose failure was associated with a malnutritional state, in whom diuresis occurred from bed rest and a nutritious diet alone. Some of these patients show only slight change in the plasma chloride level. In others an extraordinary fall in blood plasma chlorides takes place and it does so unpredictably. Because of the frequency of such a response we advocate the use of ammonium chloride in doses of 4 to 6 gm. by mouth during the period of the most marked diuresis in the treatment of congestive failure. This recommendation is made not for the purpose of potentiating the diuretic effect of other agents but for its value in replacing chloride.

Much has been written about the low-sodium syndrome. It is most commonly encountered in patients in the terminal stages of heart failure. The treatment of this condition presents something of a problem. When we encounter it we attempt to correct it by giving the patient salt by mouth, or small amounts of hypertonic saline by intravenous injection if the patient cannot take material by mouth. I must say that we have not been impressed with the improvement which results from the administration of sodium chloride in these patients. However, we do attempt to correct hyponatremia when it is detected.

DR. GOLD: It is pleasant to find Dr. Luckey's experience in general agreement with the formulation of the treatment of congestive failure which we published several years ago. You have probably become aware of some points of divergence and perhaps this is a good time to see how some of the disagreements have come about.

In order to get the discussion under way I should like to refer back to a few of these points. With regard to the definition of congestive failure, I wonder what Dr. Luckey would think about defining it as a metabolic state in which the essential abnormality is an abnormal retention of salt, in consequence of which water is retained and a state of hyperhydration results. The primary seat of the trouble lies in a disturbed function of the heart but there ensue the secondary circulatory changes involving a diminished capacity of the kidney to excrete salt. Such a definition does not involve us with the abstruse nature of heart muscle weakness because there are states of extreme heart muscle weakness, as after acute coronary thrombosis, in which the circulatory abnormality is quite different. There is no congestive failure. There is only peripheral circulatory shock. The treatment in this state of extreme heart muscle weakness is quite different from that of congestive failure. The definition I propose also helps to direct attention to the center of the objective in treatment, namely, measures that will help the organism get rid of and stay rid of excess extracellular fluid, salt and water. With such a formulation as I have proposed, measures for dehydration become the first order of business. This does not eliminate digitalis to increase the contractile power of the heart. I agree with you that it is extremely important. It should be tried in every case but there is the fact that there are many cases of congestive failure, especially many with a normal sinus rhythm, in which digitalis is not very effectual and in which only after active diuretic medication with salt restriction is the condition brought under control. I myself fancy this formulation of the issues in the therapy of congestive failure over the more conventional one which you described. Since we both seem to be doing pretty much the same sort of thing in treatment, I suppose the difference in definition loses some of its importance.

I wonder if we could have some discussion of Dr. Luckey's practice to let the patient's call for water decide the issue of how much water

the patient will receive during the management of congestive failure. I once discovered that when I allowed patients to do that they usually took very little water, a total of a glass or two a day of fluid. This is partly due to the fact that people generally do not drink much water and partly to the fact that the patients seem to be afraid to drink water when they know themselves to be waterlogged. I agree with Dr. Luckey that the outcome is pretty much the same, even if one pays no attention to this item, in the milder cases of congestive failure. However, there are the occasional cases in which the success of treatment is halted by inadequate water, and by boosting the water intake the diuretic response is re-established. It is our practice to order a total fluid intake of from 2,000 to 3,000 cc. through the fluids in the food and other fluids including water. This insures that most patients will be receiving at least what the average normal person takes in the form of available water through free fluids and normal solid food intake. Although Schemm has found that treatment with huge quantities of water is sometimes helpful, we have not encountered any need for that method of approach.

Dr. Luckey agrees that the daily dose of the mercurial is safe and advocates what seems to me a reasonable approach to avoid excessive dehydration by following the period of daily dosage with a period in which the interval between doses is prolonged. I question the wisdom, however, of his limiting the daily dosage to the first two or three days for, while this will probably do in the majority of milder cases, it will unnecessarily reduce the efficacy of the system in the patient with advanced congestive failure who has about 60 pounds of edema fluid to lose. Is it not wiser to advocate a more elastic plan, as we have done, the use of the daily dose until the body weight reaches close to the "dry level" and then begin to spread the interval? For the milder cases that will turn out to be only a few days but may well extend over a period of two weeks or even longer in the more severe and advanced cases. Such an approach can only be advantageous. I think that Dr. Luckey will agree that no aspect of this treatment should be arbitrary. The dose of the mercurial, the interval between injections and the duration of the daily dose should be determined by the response of the individual patient.

Then there is the question of the milk diet. At the beginning of the treatment we advocate one glass of milk and one glass of water at intervals of an hour alternately for a total of four to six glasses of each, giving a total of 2 to 3 L. of fluid and, with the larger amount, about 1,000 calories in the form of milk, representing approximately 1.5 gm. of salt. Dr. Luckey does not look upon milk as a satisfactory initial diet because most adults are relatively intolerant of milk, patients complain of not having enough to eat, because milk is not as low-salt a food as many other articles of diet and because to get low-salt intake with milk requires excessive restriction of calories. I wonder about these objections to milk. I have not found most adults intolerant of milk. They seem to tolerate it very well. They do not like it as a steady diet, but then most patients with congestive failure do not require it for more than a period of several days. In our series of nearly 150 patients with congestive failure reported several years ago the "dry weight" was reached in an average period of six days, some shorter, some longer; right after this we put them on a mixed diet. I find that most patients with advanced congestive failure will tolerate the inconvenience of a milk diet for several days, with the prospect ahead of rapid relief from their suffocation and cough. There are a few who develop diarrhea or vomit, or who have some psychologic obstacle to taking milk. In these we use a mixed low-salt diet or some modification of the so-called rice diet. I do not know whether milk has any special diuretic properties but our turning to milk arose from the fact that low-salt diets are not very easy to carry out even in well organized hospitals. The patient sometimes calls our attention to the salty taste of some of the food and it was not at all rare to find that the maid, in following a routine practice, had overlooked the special situation and had put the salt cellar on the tray. I have no objection to a low-salt mixed diet when one can be quite certain that lapses can be prevented. I wonder about the practical significance of the objection that there are foods that have even less salt than milk and that to get a low enough low-salt diet with milk requires excessive reduction of calories. Dr. Luckey referred to the standard caloric requirement of 25 calories per kg. of body weight. A patient weighing 70 kg. would, with this formula, receive 1,750 calories a day. Do we want to put a patient who is at complete rest in the initial phase of the treatment of congestive

failure on such a high caloric intake? Is it not desirable to reduce the caloric intake to something closer to 1,000 calories a day in the early days of treatment? I believe that reduced caloric intake is one of the conventions in the treatment of congestive failure at the start. A quart and a half or 1.5 L. of milk a day gives the patient about 1,000 calories with an average salt intake of 1.5 gm. I agree with the point implied by Dr. Luckey that it is not desirable to apply starvation in the long-term treatment and maintenance of the patient with congestive failure, but the issue of the use of milk refers only to a period of several days in the vast majority of cases.

Perhaps we might have some questions from the audience and Dr. Luckey might answer them all at one time.

DR. HAROLD E. B. PARDEE: I should like to comment about the patient you referred to, who had 60 pounds of edematous fluid to lose. I am inclined to avoid proceeding too rapidly in getting a patient of that kind free of edematous fluid. I tend to slow down the process even if I find it possible to get rid of 2 or 3 pounds of weight a day. Certain disturbing symptoms appear, such as drowsiness and other discomforts, which may be related to rapid loss of sodium. The reactions are not serious and they are readily corrected by halting the diuretic treatment. It seems to me that these patients have to make extensive physiologic adjustments when such large quantities of fluid and electrolyte are lost from the body, and it seems to me wise to allow them to make those adjustments gradually.

In connection with the general application of the plan of treatment that was outlined, I think it is well to bear in mind the fact that congestive failure does not as a rule come on suddenly, and there are a great many patients with diminished cardiac reserve in whom the more usual signs of congestive failure are absent. I am not certain that everyone would regard them as in congestive failure, yet they are in congestive failure and present congestion in the lungs, the liver and other tissues. There is no sharp line of separation. These early cases often go without treatment. It is important to recognize them and to apply the newer measures which have been discussed. The treatment does not need to be so intensive. The patient may not have to be placed at complete rest. He may be able to get along with salt restriction alone or with salt restriction and ammonium chloride by mouth.

DR. JOHN S. LADUE: I find it difficult to accept the stress that is placed on elimination of salt and the intensive use of mercurial diuretics. My own experience leads me to a more conservative approach. When patients with congestive heart failure are well digitalized the venous pressure falls, the vital capacity rises and the circulation time declines to normal. These changes are evidence for the fact that the congestion we have to worry about, namely, the pulmonary congestion, is under control. I do not believe that persistence of the peripheral edema does the patient any particular harm. We followed up a large number of patients in heart failure as severe as those who received the mercurials and found that with rest and digitalis alone the onset of compensation was rapid, adequate compensation occurring within a period of about eight days. These were patients in whom the venous pressure was above 25 cm. of water.

Then there are the patients with normal sinus rhythm. We studied a group of these and found that digitalis and rest in bed alone established satisfactory compensation in 80 per cent of them.

Diuresis always follows a reduction in the venous pressure in patients with congestive failure. We took daily venous pressures in a group of patients and found that the venous pressure fell below 15 cm. of water before any evidence of diuresis appeared. This suggested to us that improvement in cardiac efficiency, as indicated by Dr. Luckey, is the primary factor in the management of these patients. Diuretics are important when the pulmonary congestion cannot be controlled by these measures alone. Their importance is much less in connection with the peripheral edema, for this tends to subside over the period of two to four weeks, which is the usual duration of the rest period for the kind of patient with congestive failure that Dr. Luckey has discussed.

DR. PHILLIPE V. CARDON, JR.: I would like to support the point made by Dr. LaDue concerning the importance of digitalis to increase the cardiac output. We made a number of hemodynamic measurements in a few patients with left ventricular failure in whom there either was no peripheral edema or in whom the peripheral edema was controlled by diuretics. These patients continued to show a low cardiac

output. Digitalis decreased the pulmonary venous pressure and increased the cardiac output markedly. I think that the work of Stead and others in relation to sodium and water retention has resulted in too much emphasis on this factor in congestive failure and that we are getting back to the heart again.

DR. GOLD: If I understand you correctly, what you are saying is that there are patients in congestive failure who, when dehydrated by salt restriction and the mercurials alone, still continue to show evidence of failure, that these patients require digitalis and that more improvement follows digitalization.

DR. CARDON: That is correct.

DR. GOLD: That simply means that there are many patients who require both digitalis and the mercurial diuretics and salt restriction.

DR. CARDON: Yes, but perhaps digitalization is the most important factor.

DR. GOLD: That digitalis is the most important factor does not follow from the experience you presented. To refer to digitalis as more important would require an altogether different kind of evidence.

DR. CARDON: The point I tried to make is that without digitalization, without this effect on the heart, one can demonstrate that the state of congestive failure still exists physiologically.

DR. GOLD: Again then, what you say is that patients in congestive failure need digitalis.

DR. CARDON: Yes, and perhaps that digitalization may do the job without the mercurials.

DR. GOLD: We can, of course, look at the other side of the story and say that many of these patients do very well without digitalis and with salt restriction and the mercurials alone. The fact is that there are both kinds of patients, those who do very well with digitalis alone without the diuretics and those who do very well with the diuretics alone without digitalis. I think the only reasonable approach to this situation is to use both measures, as we have advocated in the routine management of congestive failure, since one cannot distinguish these patients in advance. Which of these factors the patient can do without may then be determined for each patient in the course of time and adjustments can then be made accordingly. That seems to me to be the most practical approach to the practical problem.

DR. CARY EGGLESTON: I agree in general with the things that have been said. All the factors which present themselves in congestive failure have to be taken into consideration in every patient, and in the end the kind of treatment depends on the doctor's judgment of their relative importance in the whole picture of the particular patient. Moderate restriction in salt is often very important. The use of digitalis is paramount in most instances. A considerable number of patients, if undigitalized and kept at rest in bed and limited in their salt intake, will recover.

DR. MACK LIPKIN: I was intrigued by Dr. Luckey's opening remarks concerning the factors which precipitate an attack of congestive failure. In a series of patients observed at the Cincinnati General Hospital some years ago a surprisingly large number were found who themselves attributed their attack to a violent, often prolonged, emotional upheaval. If this is so, it would seem to me important to make an attempt in the matter of rest to achieve not only physical but psychic rest as well.

DR. GOLD: I believe that one cannot emphasize too strongly the importance of that point. An emotional upheaval is commonly the factor which precipitates an attack of pulmonary edema with left heart failure in the hypertensive patient. This precipitating factor is also frequently seen in patients with rheumatic heart disease and mitral stenosis. Such patients often carry on very satisfactorily with what appears to be ample reserve for physical work and then in relation to some emotional upset develop an attack of pulmonary edema. This does not happen to be acute left ventricular failure but pulmonary edema due to the sudden increase in blood flow through a narrow mitral valve with high pulmonary vascular pressure. This is not congestive failure although it is often referred to as congestive failure. It is not helped by digitalis. Salt restriction and vigorous diuretic therapy are extremely helpful in such cases, both in treating the attack and preventing recurrences. It is, therefore, of some practical importance to consider the fact that the trouble may not lie in failing muscle but in mechanical obstruction at the valve. Here diuretics help and digitalis does not.

May we hear more from you now, Dr. Luckey?

DR. LUCKEY: As to the definition of congestive failure, I believe it is a misdirection of our interest if we do not include in it the heart as the primary site of the difficulty. I think it is a mistake to define it as a metabolic disturbance

involving salt and water because there are other metabolic disturbances in this condition such as oxygen lack and lactic acid acidosis. Lactic acidosis may be a very important factor although it has not been adequately investigated.

As to the amount of water the patient receives, I can only repeat our view that it is of no importance in the patient with heart failure who is having good diuresis. There are situations where the patient is not having diuresis, where the edema persists and the urine volume falls off when the amount of ingested fluid is too small, in which I boost the water intake up to 2 or 3 L. a day. In most instances I see no reason for doing more than allowing the patient's thirst to decide the amount of water.

My reason for limiting the daily mercurial to a period of three or four days is the fact that I was talking about the average patient. The average weight loss in our experience with the group of patients I mentioned before was about 24 pounds and it took an average of six days to reach this point. It is interesting that in ten patients who received the same regimen without the mercurials the average duration to the point of recovery was also six days, but I should mention that these were selected patients and the edema in this group was less, as shown by the lower total weight loss. Of course if the patient continues to have an active diuresis, it is our practice to continue the daily mercurial until the weight begins to approach the optimum level.

DR. GOLD: If that is what you do, then we are in complete agreement.

DR. EGGLESTON: I would like to ask what dose of the mercurial you use. Do you give a dose that produces profuse diuresis, or a moderate one, or a minimal diuretic effect?

DR. LUCKEY: We generally use 2 cc. of the mercurial diuretic from the very start. Smaller doses at the start have been recommended by some. We have continued that dosage for long periods of time. We have not been concerned with the matter of too rapid loss of fluid. I am not convinced that it is a source of any particular trouble in these patients.

I would also like to call attention to the fact that digitalis is of paramount importance in patients with auricular fibrillation. We have observed that in patients with auricular fibrillation and a rapid heart rate, no matter how much salt restriction is used or how often mercurial diuretics are given the weight often continues to rise but the condition is promptly brought under control when the patient is adequately digitalized.

DR. GOLD: That accords with my experience.

DR. WALTER MODELL: I would like to address this question to Dr. Luckey. We have heard several views expressed here today concerning the treatment of congestive failure and I wonder if he can see any more difference between them than I seem to. The differences seem to me to be simply in the order in which the measures are applied and perhaps the intensity of the treatment.

DR. GOLD: Dr. Luckey, do you see any other difference?

DR. LUCKEY: Very little difference.

DR. LADUE: I wonder if Dr. Luckey would say something about the use of morphine and related drugs in the management of the dyspneic patient with congestive heart failure.

DR. LUCKEY: Sedation is a valuable measure for securing rest in these patients. Morphine is often one of the most important agents at the beginning. It has been found to interfere to some extent with the diuretic effect of the mercurials but I believe that this is far outweighed by the benefits of alleviating anxiety. One should warn, however, about the group of patients with chronic pulmonary disease who may also have right-sided failure. They are apt to be intolerant of morphine and this drug, even in small amounts, sometimes produces disastrous respiratory depression.

DR. CARDON: I would like to add a word on the side of the suggestion implied by Dr. Pardee and Dr. LaDue concerning the desirability of avoiding too much fluid loss in a twenty-four-hour period. When you talk to a patient who has had a very marked diuretic response to a dose of the mercurial the day before, you often find that the first thing he comments about is the fact that he was up all night and did not get a bit of rest. It can be a very stressful experience for the patient to have to call for the bedpan every few minutes.

DR. GOLD: Why not give the dose of the mercurial early in the morning? If you do this, of course, he is not likely to be disturbed so much during the night.

DR. CARDON: Not exactly, because the effect of the dose often extends on through the night.

DR. GOLD: The fact remains that the patient is there for the treatment of congestive failure, and the inconvenience of being up several times

during the night in the first few days is not too big a price to pay for relief from suffocation.

DR. CARDON: But if the patient is not suffering especially and he is going to be in the hospital a few weeks, it is not necessary to wring the edema out of his legs so rapidly.

DR. GOLD: I suppose we would all agree that it is well not to wring it out too rapidly. I think if one adjusts the system of treatment so as to secure a daily weight loss of no more than 2 or 3 pounds, it is not likely to be too rapid.

SUMMARY

DR. GOLD: The discussion in this conference on the management of congestive failure may be summarized under two headings: (1) mechanism, and (2) details of treatment. There are those who look upon congestive failure as a condition having its origin in myocardial weakness which results in secondary renal and other effects giving rise to edema and other manifestations having a similar meaning; in relation to this viewpoint, administration of digitalis to enhance the function of the heart is considered the primary point of attack in treatment, salt restriction and diuretic agents serving as adjuvants. The alternate viewpoint does not exclude the essential elements of this formulation but shifts the focal point of attention to the metabolic disorder, salt and water retention. In this case one takes the position that although the salt and water retention is secondary to failure of heart muscle, it often assumes a high degree of autonomy in the clinical syndrome of congestive failure, so that digitalis to strengthen the heart muscle has in some cases relatively little effect in clearing the state of hyperhydration and the clinical condition is brought under control only by the use of potent diuretic agents. The reason stated for advocating this view is the belief that the major share of the credit for the marked improvement in the results of the treatment of congestive failure in recent years is to be ascribed to the early and intensive application of measures designed to enhance the excretion of salt and water through salt restriction and active diuretic therapy.

There seemed to be no disagreement on the point that patients with congestive failure should be treated with restricted activity, a digitalis preparation, salt restriction in the diet and diuretic agents. Differences of opinion arose chiefly on matters of the details of the application of these measures, but these details are very important and often decisive. What is the most appropriate diet for the short-term and the long-term restriction of salt intake? What are the advantages and disadvantages of milk in the treatment of the acute phase of congestive failure? Should water be restricted or given freely? What decides the amount of fluid the patient should be allowed? How well do patients do with salt restriction and the diuretic agent without digitalis? What is the best dosage plan for the mercurial diuretic? How rapidly should one attempt to clear the patient of edema? These and related questions were the subject of spirited discussion. Special attention was paid to the problem of overtreatment, the low-salt syndrome, the very early case of congestive failure without the usual manifestations, and the special problems of the resistant cases.

Clinico-pathologic Conference

Myelofibrosis and Extramedullary Hematopoiesis

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, J. D. (No. 60914), was a merchant, forty-three years of age, who was first seen on April 26, 1950, in the Hematology Division of the Department of Medicine. He gave a history of increasing fatigue and lassitude during the previous five years. For three to four months he had noted increasing anorexia and morning nausea without vomiting. For two months he had been troubled by chilly sensations and on a few occasions had actually experienced shaking chills without fever. He had lost 12 pounds in the three months immediately past.

The family history was non-contributory. The past history was of interest because in 1944, while the patient was in the Army, he was found to have an enlarged spleen and was shortly thereafter given a medical discharge. No further information about his Army record was available. In 1946 he acquired syphilis; intramuscular and intravenous injections were given for one year. There was no other history of exposure to toxins.

The significant physical findings included slight pallor of the skin and mucous membranes, a few petechiae over the right shoulder and several old scars from war injuries on the right thigh and left shin. The firm, non-tender spleen extended 8 cm. below the left costal margin.

Laboratory data obtained in April, 1950, were as follows: red blood cell count, 4,040,000; hemoglobin, 14 gm. per cent; white blood cell count, 14,400; differential count, 8 per cent basophils, 7 per cent metamyelocytes, 22 per cent C myelocytes, 1 per cent A myelocytes, 24 per cent band forms, 29 per cent segmented neutrophils, 7 per cent lymphocytes and 2 per cent monocytes; platelet count, 230,000; reticulocytes, 5.1 per cent. There was moderate anisocytosis and poikilocytosis of the red blood cells.

Attempts were made to aspirate bone marrow from the sternum, the manubrium and the spinous process of a vertebra. On each occasion the marrow cavity was entered without difficulty but no cellular clumps were obtained. A diagnosis of myelofibrosis with extramedullary hematopoiesis or of chronic myelocytic leukemia was entertained, and the patient was referred to the Barnes Hospital on May 30, 1950, for sternal biopsy.

His physical findings and laboratory data were unchanged from those noted previously. The biopsy was accomplished without difficulty and the patient was then discharged from the hospital. Histologically, the surgical specimen revealed thickened trabeculae with fibrous replacement of the marrow cavity and essentially no hematopoietic tissue; these changes were considered confirmatory of the diagnosis of myelofibrosis.

No specific therapy was given. The patient continued to feel weak and tired, but his appetite increased and he gained some weight. He complained of occasional pain in his shoulders and legs.

The second admission to the Barnes Hospital in September, 1950, was arranged in order that the presence of extramedullary hematopoiesis in the spleen could be demonstrated, and a trial of corticotropin therapy could be given. Laboratory data were as follows: red blood cell count, 4,180,000; hemoglobin, 11.4 gm. per cent; white blood cell count, 7,800; differential count: 3 per cent basophils, 3 per cent A myelocytes, 2 per cent B myelocytes, 8 per cent C myelocytes, 6 per cent metamyelocytes, 15 per cent band forms, 47 per cent segmented neutrophils, 13 per cent lymphocytes and 3 per cent monocytes; platelets, 209,000; reticulocytes, 5 per cent. There were 2 normoblasts and 1 late erythroblast per 100 white blood cells; moderate

anisocytosis and poikilocytosis were again noted.

The splenic edge was palpable 10.5 cm. below the left costal margin and splenic puncture was performed uneventfully. The biopsy specimen showed marked extramedullary hematopoiesis. Corticotropin, 40 mg. three times daily, for six days was administered intramuscularly; therapy was then changed to cortisone, 100 mg. daily. Aside from a slight rise in the red blood cell count there was no change in the blood findings.

Following his release from the hospital the patient continued to take 100 mg. of cortisone by mouth daily; he felt generally better, gained strength, had an increased appetite and continued to gain weight without developing edema. Laboratory data obtained on November 21, 1950, were as follows: red blood cell count, 4,240,000; hemoglobin, 10.7 gm. per cent; white blood cell count, 8,300; differential count, 6 per cent basophils, 1 per cent eosinophils, 10 per cent myelocytes, 5 per cent metamyelocytes, 14 per cent band forms, 47 per cent segmented neutrophils, 12 per cent lymphocytes and 3 per cent monocytes. Urinalysis: negative except for the presence of 6 to 8 white blood cells per high-power field in the centrifuged sediment. Stool: negative for occult blood. Blood chemistry: non-protein nitrogen, 11 mg. per cent; icterus index, 5 units; cephalin-cholesterol flocculation, 1 plus; thymol turbidity test, 3.3 units; alkaline phosphatase, 2 Bodansky units; total protein, 6.7 gm. per cent, albumin 4.3 gm. per cent; globulin, 2.4 gm. per cent.

The patient continued to take cortisone intermittently and was reasonably well until two months prior to his final admission when he began to have increasing dyspnea, anorexia, weight loss and low-grade fever. In addition, he developed pain over the spleen which, during the month prior to his admission, had become so severe that he was virtually incapacitated and required increasing amounts of narcotics for relief. He also noted swelling of the left testicle. During this period his red blood cell count and hemoglobin fell and he had to be given three transfusions. He was admitted for the last time on May 30, 1952.

Physical examination revealed his temperature to be 36.1°C., pulse 108, respirations 20 and blood pressure 108/68. He showed evidence of recent weight loss. His skin was pale but there were no petechiae and no edema. Examination of the eyes, including the optic fundi, was not remarkable. The upper respiratory tract appeared normal. There was no generalized lymph node enlargement but several non-tender, easily movable lymph nodes, 0.5 to 1.0 cm. in diameter, were noted in either axilla. The chest was clear to percussion. A few fine rales were heard at the right base posteriorly. Examination of the heart revealed it to be normal in size and contour. The sounds were of good quality, and there was a grade 2 soft apical systolic murmur. The spleen was firm, very tender, and extended to the iliac crest and into the right lower quadrant. The liver edge was palpable at the costal margin on the right. The left testicle was enlarged and the spermatic cord on the left was thickened. Aside from slight edema of the ankles the remainder of the examination was within normal limits.

The laboratory data were as follows: red blood cell count, 2,760,000; hemoglobin, 6.9 gm. per cent; white blood cell count, 4,950; differential, 3 per cent basophils, 1 per cent A myelocytes, 13 per cent C myelocytes, 2 per cent metamyelocytes, 16 per cent band forms, 55 per cent segmented neutrophils, 8 per cent lymphocytes and 2 per cent monocytes; there was moderate anisocytosis and poikilocytosis of the red cells and an occasional nucleated red blood cell was seen; platelet count, 188,000. Urinalysis: specific gravity, 1.013; protein, negative; sugar, negative; sediment, many red blood cells per high-power field. Stool: guaiac negative. Cardiolipin test: negative. Roentgenogram of the chest: discoid atelectasis at both bases with elevation of both diaphragms and bilateral pleural effusion. Roentgenograms of the pelvis: dense, slightly irregular sclerosis of all the bony structures was noted, and was thought to be compatible with myelofibrosis. Electrocardiogram: sinus tachycardia.

The patient was extremely uncomfortable and had considerable dyspnea throughout the period of hospitalization. He complained of excruciating pain in the left upper quadrant, over the spleen; the pain was so severe that he was comfortable only when he was absolutely still. It was the consensus that the pain arose as the result of multiple splenic infarctions and/or perisplenitis. Because the pain was intolerable, and because it was believed that the patient probably was forming considerable amounts of blood at sites other than the spleen, splenectomy was performed on June 11, 1952. Following surgery the patient did well for three days. The

white blood cell count reached a maximum of 38,500 without significant change in the differential, and the platelet count increased approximately 1,000,000 per cu. mm. On June 14th, however, he began to have a low-grade fever and gross hematuria. Soon thereafter ankle edema and signs of ascites were noted. The patient's urinary output decreased markedly. A urologic consultant thought that myeloid infiltration of the kidney probably explained both the gross hematuria and the oliguria; because of the patient's condition cystoscopy and pyelography were deferred. The abdomen became increasingly distended. A double lumen tube was introduced into the stomach for purposes of decompression, and the patient was also given feedings parenterally. A roentgenogram of the abdomen revealed changes consistent with postoperative pneumoperitoneum and adynamic ileus.

Antibiotic therapy which had been started the day prior to splenectomy was continued, but the patient failed steadily. The non-protein nitrogen rose from normal to 95 mg. per cent on the twelfth postoperative day at which time the sodium was 127.9 mEq./L., potassium, 5.7 mEq./L., carbon dioxide combining power, 24.4 mEq./L. and chloride, 88 mEq./L. On the thirteenth hospital day the carbon dioxide combining power had fallen to 21.1 mEq./L and the patient was given a liter of one-sixth molar sodium lactate intravenously. Urinalysis revealed a specific gravity of 1.009, 2 plus proteinuria with many erythrocytes, white blood cells and bacteria in the centrifuged sediment. Acute pyelonephritis was suspected. The patient's urinary output increased slightly during the last few days of life, but his temperature rose steadily to 39.8°C. and he became increasingly obtunded. He died on June 25, 1952.

CLINICAL DISCUSSION

DR. CARL V. MOORE: This patient initially presented a problem in diagnosis. The hematologic changes in the peripheral blood could have been due either to myelocytic leukemia or myelophthisic anemia. Dr. Ackerman, will you tell us how the bone marrow obtained by trephine biopsy of the sternum differentiated between these two possibilities.

DR. LAUREN V. ACKERMAN: The differentiation between myelocytic leukemia and myelophthisic anemia from whatever cause is often difficult, especially if one relies on bone marrow aspiration. On the other hand, it is relatively simple if surgical biopsy is performed. Thus in this case the small segment of marrow sent to us showed increased fibrous tissue, very little evidence of hematopoetic activity and an increase of bony trabeculae. No evidence of malignant disease or of leukemia could be found. A diagnosis of myelofibrosis and myelosclerosis was made in the surgical pathology laboratory.

DR. MOORE: Dr. Ackerman, you used the terms myelofibrosis and myelosclerosis. How do those two differ?

DR. ACKERMAN: Myelofibrosis involves the connective tissue between the bony trabeculae whereas myelosclerosis refers to the thickening of the bony trabeculae themselves.

DR. MOORE: You prefer these terms to osteosclerosis?

DR. ACKERMAN: That is a matter of semantics, but I think that myelofibrosis and myelosclerosis are preferable to the term osteosclerosis.

DR. MOORE: Splenic biopsy demonstrated the presence of extramedullary hematopoiesis, so that both that diagnosis as well as the diagnosis of myelofibrosis were confirmed before the patient's death. Dr. Elliott, will you review the x-ray findings and indicate whether they are compatible with the clinical and pathologic diagnoses made.

DR. GLADDEN V. ELLIOTT: The roentgenographic findings fit well with Dr. Ackerman's description of the pathologic change in the bone marrow; throughout the pelvis, ischium, ilium and both proximal femurs as well as in the lumbar spine there was a striking increase in the density of bone. Closer examination revealed that the increased density was irregular, patchy and similar to that seen in bony metastases from carcinoma of the prostate or with bony involvement in Hodgkin's disease or other lymphomas. I do not believe there is any simple way to differentiate these various conditions on the basis of the radiologic changes. The marked elevation of the diaphragms and the increase in soft tissue density in the upper abdomen probably were attributable to enlargement of both liver and spleen. The elevated diaphragms produced several areas of discoid atelectasis at both lung bases. These were present in all films made during the patient's illness. A film of the abdomen taken prior to splenectomy was notable for the huge spleen, the tip of which could be seen projecting below the iliac crest. After operation

another film of the abdomen revealed that the liver was also large.

DR. MOORE: Dr. Elliott has indicated that the roentgenographic changes were at least compatible with the diagnosis which was made on the basis of bone marrow biopsy. Dr. Loeb, when one sees a patient with myelofibrosis he needs to determine whether the myelofibrosis is primary or secondary. How is that differentiation made and under what conditions may myelofibrosis be secondary?

TABLE I
MYELOFIBROSIS

I. Focal
  A. Primary
  B. Secondary
    (various congential bone diseases, Paget's disease, about sites of bone tumors)
II. Generalized
  A. Primary (idiopathic)
  B. Secondary
    (various bone diseases, metastases to bones, myeloma, polycythemia, leukemia, Hodgkin's disease, Gaucher's disease, amyloid disease, xanthomatosis, septicemia, tuberculosis, renal disease, poisonings, (benzene, fluorine, chronic irradiation, experimental)

DR. VIRGIL LOEB, JR.: The easiest way to answer your questions, Dr. Moore, is to refer to a classification (Table I) which we have adapted from that of Erf and Herbert.[1] We have found this schema convenient to use although it may not be completely accurate. As has been pointed out, the patient under discussion today demonstrated the roentgenologic changes characteristic of generalized myelofibrosis. However, there are certain individuals who manifest x-ray evidence of focal areas of myelosclerosis. These focal areas may be primary and of unknown etiology or may simply be localized areas of increased bony deposition in the normal medullary space of the bone marrow. Focal lesions may also be secondary to various bone diseases, as noted on the outline.

Generalized myelosclerosis or myelofibrosis may also be divided into a primary and secondary type. The former is the condition with which we are presumably dealing today. There is no obvious etiology for the disease in this particular case. It developed insidiously and without evidence of a precipitating or etiologic agent; for this reason it is classified as primary idiopathic generalized myelofibrosis.

The secondary types of myelofibrosis are perhaps recognized more frequently. The various conditions which may presumably cause generalized secondary myelofibrosis are indicated on the outline. Most of these are self-explanatory, although I think it is important to emphasize that tuberculosis may be accompanied by a myelosclerotic reaction of the bone marrow. We have records on one such case. Various toxic agents can cause deposition of fibrin and ultimately bony tissue in the medullary space. There are also experimental means of producing myelofibrosis, on one of which I believe Doctor Bukantz can comment.

In the present limited state of knowledge concerning the pathogenesis of myelofibrosis, differentiation of the primary and secondary varieties can be made only from a careful history and evidence of contact with a specific etiologic agent. Those patients in whom no etiologic factor can be incriminated are called primary or idiopathic. Subsequent experimental work may prove that much of what we now call primary myelofibrosis will ultimately be found to represent a secondary reaction.

DR. MOORE: Dr. Bukantz, would you say something about the production of myelofibrosis experimentally?

DR. SAMUEL C. BUKANTZ: It is of interest that if one searches through the literature concerning various diseases of unknown etiology one usually can find the suggestion that the cause may be "allergic." Thus when I surveyed the literature on myelofibrosis I was not surprised to find an article in the Scandinavian literature bearing on this point. Reference is made to unpublished work said to have demonstrated that repeated intramuscular and intravenous injections of egg albumin into rabbits produced a disease analogous to myelofibrosis in man. The animals exhibited diffuse severe myelofibrosis, anemia and peripheral blood changes. The development of this entity was interpreted as having resulted from the absorption of antibodies on the cells with subsequent antigen-antibody reaction when antigen was introduced in larger amounts. Because, as I have indicated, the actual experimental work was unpublished it is very difficult to evaluate it. Dr. Germuth has been interested in experimental hypersensitiveness and I wonder whether he has encountered any changes suggesting myelofibrosis in his animals?

DR. FREDERICK G. GERMUTH: I have observed hyperplasia of reticulum cells and granulomas in the bone marrow but no fibrosis.

[1] ERF, L. A. and HERBERT, P. A. Primary and secondary myelofibrosis. *Ann. Int. Med.*, 21: 863, 1944.

DR. MOORE: As I mentioned at the outset of the discussion, cases of this type present the problem of differentiation between myelofibrosis and leukemia. We have decided in favor of myelofibrosis, but basophils were often increased in the patient's peripheral blood and many hematologists hold that all cases of myelofibrosis, not readily explained on some obvious basis, are in reality unusual forms of leukemia. Dr. Harrington, would you comment on this point of view?

DR. WILLIAM J. HARRINGTON: Although it is true that a considerable number of hematologists believes that so-called agnogenic myeloid metaplasia is a variety of sub-leukemic chronic myelogenous leukemia, an equal or perhaps greater number considers myelofibrosis to be an entirely separate entity unrelated to leukemia. In my experience, the "typical" patient with agnogenic myeloid metaplasia has a considerably greater number of nucleated red blood cells in the peripheral blood than the patient with myelogenous leukemia, assuming an equivalent white blood cell count. Often patients with myeloid metaplasia fail to exhibit basophilia, and usually they do not have a marked degree of anemia early in the course of the disease. In general, patients with myelogenous leukemia have a life expectancy of only a few years. On the other hand, patients with agnogenic myeloid metaplasia may live for eight to ten years and many go on for much longer periods of time. Nonetheless, differentiation between the two may be extremely difficult, although personally I believe that they are separate entities. We have often discussed the interesting fact that some patients with myelofibrosis have extramedullary hematopoiesis whereas others do not. I believe it is your view that the occurrence of myeloid metaplasia indicates a primary disorder of the bone marrow whereas myelofibrosis without myeloid metaplasia constitutes a primary disorder of the blood forming cells *per se*.

DR. MOORE: One certainly sees cases of myelocytic leukemia which seem perfectly characteristic clinically and yet at postmortem show myelofibrosis. Conversely, there are patients who have what seems to be classical myelofibrosis for years who die with the peripheral blood picture of myelocytic leukemia. Dr. Reinhard, do you consider these two conditions distinct entities?

DR. EDWARD H. REINHARD: I believe the present evidence suggests that they are distinct. If in the spleen one can demonstrate foci of blood formation containing megakaryocytes and nucleated red blood cells as well as immature myeloid forms, he has evidence that strongly supports the diagnosis of myelofibrosis. One does not ordinarily see infiltration of the spleen and other organs by megakaryocytes and nucleated red blood cells in myelocytic leukemia. In my opinion, perhaps the most valuable antemortem proof that a given patient has myelofibrosis and not myelocytic leukemia is the demonstration of extramedullary bone marrow formation.

DR. MOORE: This patient presented other clinical manifestations common in myelofibrosis, e.g., bone pain. It is of some interest to me, however, that he did not develop marked hepatomegaly. Very often, especially in the terminal stages of this disease, the liver becomes almost as large as the spleen, but throughout most of this patient's clinical course there were repeated notes that the liver edge extended only a few cm. below the costal margin. Dr. Reinhard, do you have any comments about this point?

DR. REINHARD: No, except that there is distinct variation in the degree of involvement of different organs by extramedullary bone marrow formation. There was a mass in the scrotum which could have been due to a venereal infection to which he had been exposed, but the possibility must also be considered that the testis was the site of extramedullary hematopoiesis.

DR. MOORE: This patient was treated with cortisone over a long period of time and, although you did not recommend x-ray therapy to the spleen, late in the course of the disease splenectomy was performed. Would you comment on the therapeutic management of myelofibrosis?

DR. REINHARD: It was with real trepidation that we performed the splenic puncture on this patient, and we recommended splenectomy only after a great deal of thought and consultation. It is well known that splenectomy is not indicated in the usual case of myelofibrosis with extramedullary hematopoiesis. Thus in a classic article in 1937, Hickling[2] described 27 patients, suffering from what he called chronic non-leukemic myelosis (a term equivalent to our agnogenic myeloid metaplasia), all of whom had undergone splenectomy. Nineteen of the patients died within several months and twenty-

[2] HICKLING, R. A. Chronic non-leukemic myelosis. *Quart. J. Med.*, 6: 253–275, 1937.

four of them within one year of the operation. Dr. Hickling concluded that splenectomy was actually contraindicated, and it is quite clear why it would be. The spleen becomes one of the major sites of blood formation in patients with this disease, not only of white blood cells but also of red blood cells; consequently, if the spleen is removed, the patient loses an important source of cellular elements. Since these patients need all of the blood cells that the extramedullary areas can produce, it is easy to understand why splenectomy is apt to be detrimental. Therefore, it should not be performed unless there is good evidence that the spleen is either depressing blood cell formation or is destroying red cells. Dr. Loeb, of course, has studied this problem for a considerable period of time and has shown how these data may be obtained and how they aid in the management of these patients.[3] The rate of red blood cell formation may be measured by studying radioactive iron utilization and determining the rate at which radioactive iron is incorporated into hemoglobin by newly formed red blood cells. If it can be demonstrated that there is an increased rate of red cell production after corticotropin or cortisone is given, splenic suppression of red cell formation may be suspected. Furthermore, the rate of red cell destruction can be measured by following the survival of normal cells transfused into the patient. In some cases increased destruction has been slowed by hormone therapy so that fewer transfusions are required. Systematic observations such as these have pointed to the advisability of splenectomy in certain highly selected instances. In the present case, although we were certain that the spleen was the site of considerable extramedullary hematopoiesis, there was presumptive evidence that the spleen was responsible in part for the pancytopenia, and we hoped that the patient would be able to maintain his red cell count and perhaps a more normal platelet level after splenectomy. We were encouraged to go ahead and recommend splenectomy because of these considerations plus the very important one that his spleen had become an almost unbearable physical burden. He suffered not only a great deal of pain but also had serious symptoms arising from the pressure of the spleen on other intra-abdominal viscera.

Dr. Moore: How good was the evidence, Dr. Reinhard, that cortisone was beneficial to this patient? After cortisone therapy was begun he developed an anemia that he had not had previously.

Dr. Reinhard: It is true that the patient developed anemia while on cortisone therapy but it is probable that the anemia reflected the progress of the disease and was not attributable to cortisone.

Dr. Moore: I saw this patient much less frequently than did Dr. Reinhard but I would like to emphasize that the pain which developed over his spleen just prior to splenectomy was excruciating.

Dr. Reinhard: That fact was of greatest importance in our ultimate decision in favor of operation; for although we had considered splenectomy previously, we never believed that the procedure was justified until the intractable pain developed. Then, because we had nothing else to offer, we were of the opinion that the operation would eleviate the pain and hoped that it might be beneficial also as far as the underlying disease process was concerned.

Dr. Bukantz: Doesn't one sometimes find evidence from the bone marrow biopsy which may be useful in determining whether or not splenectomy should be done?

Dr. Reinhard: Yes, if it can be demonstrated that the bone marrow is originally aplastic or hypoplastic and after corticotropin or cortisone there is an increase in radioactive iron utilization and restoration of a more normally cellular marrow, one is encouraged to believe that destruction of the marrow is not complete and that regeneration may be more likely to occur after splenectomy.

Dr. Bukantz: How often can adequate bone marrow specimens be obtained by aspiration and how often does one have to depend on surgical biopsy?

Dr. Reinhard: Frequently, in patients with aplastic or hypoplastic anemia bone marrow aspiration is unsatisfactory. Often in myelofibrosis, as was true with this particular patient, it is impossible to get marrow by aspiration and surgical biopsy is essential.

Dr. Moore: Dr. Scheff, the terminal episode probably can be divided into two parts, the first preceding and the second following splenectomy. Prior to operation, the patient developed anemia, fever and pain in the left upper quadrant which may have been due to splenic infarct or perisplenitis, but he also exhibited

[3] Loeb, V., Moore, C. V. and Dubach, R. The physiologic evaluation and management of chronic bone marrow failure. *Am. J. Med.*, 15: 499–517, 1953.

tachycardia, a systolic apical murmur, rales at the lung bases, enlargement of the left testicle and of the left spermatic cord and hematuria. To what would you attribute these complications?

DR. HAROLD SCHEFF: Extramedullary hematopoiesis may have developed both in the heart and the kidneys, but the possibility of bacterial endocarditis must certainly also be considered.

DR. MOORE: Perhaps the prolonged period of cortisone therapy might make bacterial endocarditis a somewhat more likely possibility. Dr. Hunter, do you care to comment on the likelihood of subacute bacterial endocarditis?

DR. THOMAS H. HUNTER: I don't think the evidence is very convincing. The patient had a significant degree of anemia and I think the apical systolic murmur could have been explained on that basis perfectly well. As you have mentioned, cortisone therapy always brings up the question of some sort of infection, but I am attracted to the possibility that there may be multiple thromboses with vascular lesions in various organs.

DR. MOORE: Dr. Harrington, Dr. Hunter has suggested the possibility of multiple thromboses and I have already indicated that splenic infarcts were suspected. Why do patients with large spleens tend to get splenic infarcts?

DR. HARRINGTON: The conventional explanations are that the splenic tissue outgrows its blood supply or that the large nodules of splenic tissue compress vessels and lead to infarcts. I am not certain that either of these is correct.

DR. MOORE: The performance of splenectomy in this patient was an heroic measure which taxed the surgeon's skill. A tremendous incision was necessary in order that the spleen could be removed.

DR. DAVID E. SMITH: The incision actually measured 33 cm.

DR. MOORE: Will you tell us, Dr. Ackerman, how the spleen appeared when it was brought to the surgical pathology laboratory?

DR. ACKERMAN: We would classify this spleen as an extremely large one. It weighed 3,200 gm. which is about twice the size of a normal liver. We were unable to find any infarcts but I must say that the diagnosis of splenic infarction is more often a clinical than a pathologic diagnosis. As a matter of fact, when I have attempted to find examples of splenic infarct in large spleens from leukemic patients I have been impressed with the difficulty of finding demonstrable infarcts. Perisplenitis, of course, is not unusual.

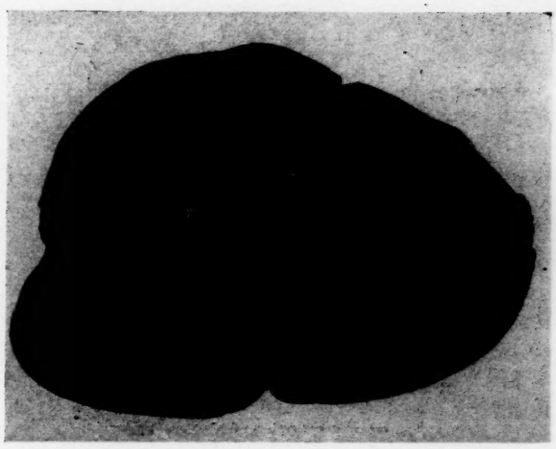

FIG. 1. A cross section of the spleen removed surgically. The large nodules of firm, pale, brown tissue within the substance of the spleen can be discerned in the lower part of the picture and were foci of extramedullary myelopoiesis. (By permission of the author, L. V. Ackerman, Surgical Pathology, C. V. Mosby Co., St. Louis, 1953.)

The most interesting gross finding was the presence of a number of nodules (Fig. 1) which were unusual in our experience and led us to think about the possibility of tumor instead of myelofibrosis. Microscopically, there was extensive evidence of both red and white blood cell formation. The sharply delineated nodular areas turned out to be almost solid masses of megakaryocytes.

DR. MOORE: Does the presence of the tumor-like accumulations of megakaryocytes suggest to you that the diagnosis is something other than idiopathic myelofibrosis, Dr. Chernoff?

DR. AMOZ CHERNOFF: No, I don't believe so. Increased numbers of megakaryocytes are common findings in myelofibrosis.

DR. MOORE: Dr. Mendeloff, let us consider the post-splenectomy period. The patient did quite well for several days. He then developed pyuria and a diagnosis of acute pyelonephritis was suggested. Subsequently, gross hematuria, oliguria, azotemia and an increase in retention of fluids was noted. Can you explain these findings?

DR. ALBERT I. MENDELOFF: It is possible that the patient may have developed acute glomerulonephritis. Certainly all of the features which you have enumerated would fit in with that disease. It occasionally does occur in patients who have undergone major surgery for reasons which are rather obscure. One other possibility to be mentioned is that extensive thrombosis in

the vena cava or perhaps in the renal vein occurred.

DR. MOORE: Dr. Reinhard, what explanation would you suggest for the terminal events?

DR. REINHARD: Prior to his death I had very little idea as to the nature of the postoperative complications. The urologist who saw him thought the hematuria might have been due to myeloid metaplasia in the kidney. I thought that explanation unlikely. We considered glomerulonephritis and pyelonephritis but were unable to be very sure about either.

DR. MOORE: Do you think he had cardiac failure?

DR. REINHARD: No, I don't.

DR. WILLIAM H. DAUGHADAY: Did he have red cell casts or any casts during this period?

DR. MOORE: There is no mention of red cell casts having been observed.

DR. JACK BARROW: Isn't it true that extramedullary hematopoiesis is demonstrated occasionally in perirenal fat?

DR. MOORE: Yes, it may be very extensive there.

DR. BARROW: With removal of the spleen do you think it possible that the amount of blood forming tissue in that area expanded?

DR. MOORE: I think it might expand but I doubt that it could have done so in four days.

DR. SCHEFF: The possibility of thrombosis of the vena cava and/or the renal vein seems a more likely explanation to me.

DR. MOORE: No summary of the clinical discussion is necessary. Most of us who cared for the man thought that he had myelofibrosis, and the consensus was that the terminal event arose because of multiple thrombi.

Clinical Diagnosis: Myelofibrosis, ? multiple thrombi terminally involving the vena cava, renal veins and ? the portal veins.

PATHOLOGIC DISCUSSION

DR. RICHARD L. SWARM: There was a large amount of clotted blood and tough, soft reddish tissue in the abdomen about the site of the splenectomy. This tissue occupied the splenic fossa and was attached to the greater curvature of the stomach. It extended inferiorly into the renal fossa and crossed behind the pancreas to involve the area back of the right kidney. All the lymph nodes in the abdomen and thorax were enlarged and contained a grossly red and pulp-like tissue similar to that in the retroperitoneal space. Thrombi filled the splenic veins and arteries. The liver was markedly enlarged, weighing 4,100 gm. This enlargement was apparently due in part to diffusely infiltrating yellowish tissue that obliterated the fine architecture of the liver in many places on the cut surface. In each kidney the abnormal soft reddish tissue surrounded the pelvis, and similar tissue was found in the left epididymis. The kidneys also showed a few flat scarred areas and, particularly in the right kidney, there were small yellow abscesses and acute pyelonephritis. The bladder contained petechiae and ecchymoses compatible with the diagnosis of cystitis. The lungs were congested and heavy. The pleural surface presented numerous fibrous adhesions, the bases of which were often buried in a soft reddish tissue similar to that in the abdomen. No thrombi or any other abnormalities were present in the lungs. The bone marrow of the femur, vertebrae and ribs appeared to be replaced by a homogeneous gray-yellow tissue which was much more compact than normal marrow and did not have a fatty appearance.

DR. DAVID E. SMITH: The remarkable soft reddish fibrous tissue in the retroperitoneal space extending from the diaphragms down to the kidneys was certainly more than an organized hematoma, yet did not have the appearance of neoplastic tissue. The first microscopic slide (Fig. 2) is from one of these areas. It shows relatively loose tissue in which are scattered fibroblasts, some cells that resemble plasma cells and others that can be recognized as myeloid cells and members of the reticuloendothelial system. The amount of fibrous tissue varies from place to place but nowhere is it the dense type of granulation tissue that might be expected to arise from irritation or infection. In some areas there are many giant cells with multiloculated nuclei, apparently megakaryocytes. It is somewhat remarkable that although erythropoiesis is easily discerned in the operative specimen of the spleen, it is difficult to find clear cut examples of erythropoiesis in the extramedullary myelopoiesis in this tissue or in the other organs examined at postmortem. Figure 3 is from one of the more fibrous and hypocellular areas of the retroperitoneal mass, and Figure 4 is from a lymph node in which the same megakaryocytic and myeloid cells again can be recognized in the sinusoids and reticular tissue. This histologic picture is almost identical with that seen in the surgical specimen in the spleen.

In the liver (Fig. 5) there are large amounts of

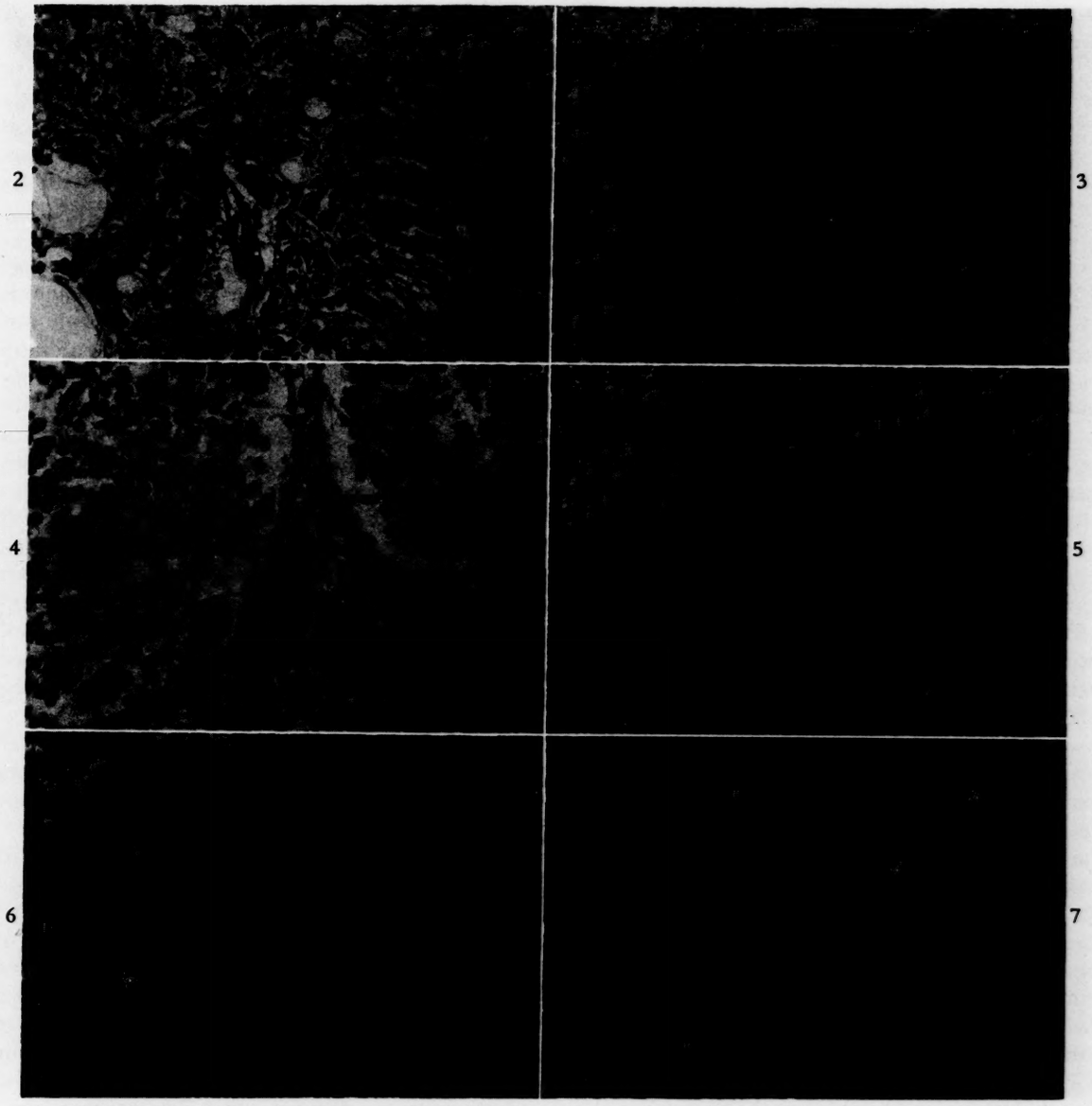

FIG. 2. The soft red tissue in the retroperitoneal space which was composed of loose fibrous tissue infiltrated by various hemopoietic elements, particularly megakaryocytes and myeloid cells.

FIG. 3. Another area in the retroperitoneal extramedullary hemopoietic tissue which is largely fibrous tissue with a light infiltration of myelopoietic cells.

FIG. 4. Lymph node showing infiltration of myelopoietic cells and megakaryocytes in the sinusoids and stroma. The spleen had an essentially identical histologic appearance.

FIG. 5. In the liver the extramedullary hemopoietic tissue is distributed as nodules in central or pericentral positions which infiltrate the sinusoids but rarely involve the portal spaces.

FIG. 6. In the kidney similar nodules of infiltration by myelopoietic tissue and megakaryocytes are present.

FIG. 7. Bone marrow of the femur is replaced by fibrous tissue in which there are a few myelopoietic cells. The trabeculae are thickened and irregular and particularly in the vertebrae there are prominent amounts of osteoid tissue about the trabeculae.

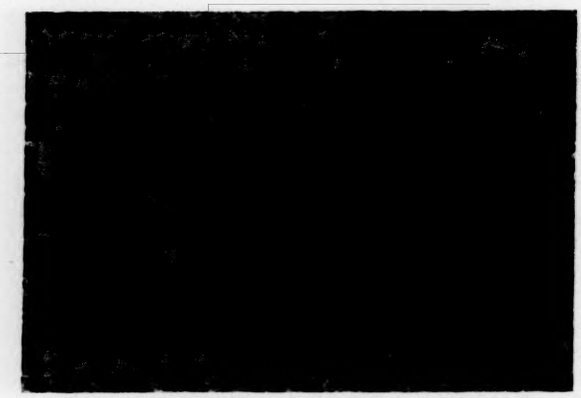

FIG. 8. Acute pyelonephritis with mature granulocytic leukocytes in the tubules and interstitial tissue.

the same type of extramedullary hemopoietic tissue. It is of a generally infiltrative character and does not prominently involve the portal spaces but is distributed focally and apparently originates within the sinusoids. This nodular appearance is somewhat in contrast to the diffuse sinusoidal and periportal infiltration typical of myeloid leukemia. In Figure 6 a section of the kidney shows the same nodular infiltration by extramedullary myelopoiesis characterized by prominent megakaryocytes. Most cases of myeloid metaplasia do not show such prominent involvement of the kidneys, and that feature has generally been contrasted to the characteristic infiltration of the kidneys in leukemia. Sections of the pleura contained the same type of tissue which extended into the lungs along the interlobular septa and even around some bronchi. The lungs, themselves, were remarkably clear of pathologic lesions. There was no pneumonia and no infarcts. In the small pulmonary vessels thrombi composed entirely of fibrin were present. It is tempting to suspect that the excess number of megakaryocytes in the extramedullary hemopoietic tissue may have had something to do with the formation of these small thrombi; however, no increase of platelets was detected during life and these were fibrin thrombi and not platelet thrombi. They were, therefore, more probably related to the congestive phenomenon and septicemia that must have occurred after the onset of the pyelonephritis.

The histologic appearance of the bone marrow is typified by Figure 7. The trabeculae are thickened and irregular and near their margins there are deposits of a lighter staining material, apparently osteoid. This is much more prominent in the vertebrae than it is in the illustrated specimen of the femur. The marrow between these trabeculae is fibrotic and contains sparse numbers of the same myelopoietic cells seen in the other tissues. It is interesting that in this disease the femur, as well as all other bones, is involved. This is a diffuse disease of the bone marrow which, as far as can be seen, involves identically those sites which are normally active as well as those which are fatty in the adult.

Figure 8 is from one of the areas of acute pyelonephritis in the kidney This involvement is extensive and there are many polymorphonuclear leukocytes in the interstitial tissue and within tubules. This cytologic pattern demonstrates that even in the terminal phase of this patient's disease his tissues were capable of mobilizing mature cells of the type that are necessary for the body defenses.

The gross and microscopic findings in this case can be summarized as demonstrating a large amount of extramedullary hemopoietic tissue, predominantly myeloid cells and megakaryocytes, involving the retroperitoneal tissues, all of the lymph nodes, the liver, kidneys, spleen and many other sites throughout the viscera. The bone marrow was replaced by thickened trabeculae and fibrous tissue; within the latter there were scattered examples of the same types of cells present in the extramedullary myelopoietic tissue.

The ultimate nature of a disease such as this in the present case has been debated for a number of years. In a typical reference, Heller et al.[4] have interpreted these findings as a variety of myeloid leukemia. They point out as suggestive of neoplasia that there are tumor-like nodules in some of the viscera and obvious infiltration of cells in many places where normal myeloid cells are not to be found. The greatest stumbling block against accepting this disease as a neoplasm or a variety of leukemia is the mixed character of the cells involved in these infiltrates. Against this argument Heller and his co-workers point out that in a fair number of cases of chronic myeloid leukemia megakaryocytes can be found in the leukemic infiltrations. They also point out that there is often irregular fibrosis of the bone marrow in myeloid leukemia. Osteosclerosis, they believe, is a perfectly understandable consequence of myelofibrosis. In essence, they say that these cases represent a combination of lesions in rather extreme form which can be

[4] HELLER, E. L., LEWISOHN, M. G. and PALIN, W. E. Aleukemic myelosis. *Am. J. Path.*, 23: 327–366, 1947.

found to a greater or lesser degree in many other cases of clear-cut myeloid leukemia.

On the other hand, other workers have interpreted this entity as a non-neoplastic, or metaplastic disease. They argue that the mixed cell type of the infiltrate is inescapably different from that of any neoplasia or leukemia, and they point to the nodular distribution of these masses of tissue within such organs as the liver as being distinctly different from the pattern of infiltration usually found in leukemia. One of the classic presentations of this idea was by Parker et al.[5] who called the entity agnogenic myeloid metaplasia.

It, therefore, seems that we must admit that histologic study of the tissues in this disease does not supply us with a final answer as to whether it is a neoplastic condition or a metaplasia in response to some unknown etiologic factor. The criteria of these two contrasting conditions are simply not sufficiently defined relative to the hemopoietic system to allow us to take a firm position. It does appear to be a primary disease of the bone marrow which in cases such as the present one leads to myelofibrosis and osteosclerosis in all sites. With the development of the lesion in the bone marrow, organs elsewhere apparently are infiltrated with extramedullary hemopoietic tissue and the supply of cells to the peripheral blood is furnished by that tissue. Cortisone has been said to stimulate the formation of extramedullary tissue; however, it is difficult to believe that it has any significant effect in this regard in most cases. Many, if not most, of the classic examples of the disease were described before cortisone was used.

Final Anatomic Diagnoses: Osteosclerosis and myelofibrosis of the femur, sternum and vertebrae; extramedullary hemopoiesis, principally myelopoiesis in the liver, kidneys, tail of the pancreas, left epididymis, pleura and interlobular septa of the lungs, retroperitoneal tissue especially of the splenic fossa and all lymph nodes; acute pyelonephritis, bilateral.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

[5] Jackson, H. J., Parker, F., Jr. and Lemon, H. M. Agnogenic myeloid metaplasia of the spleen. *New England J. Med.*, 222: 985–994, 1940.

Case Reports

Renal Function Studies in an Adult Subject with the Fanconi Syndrome*

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FANCONI[1–3] first described the syndrome characterized in children by renal glycosuria, amino-aciduria, polyuria, rickets and hypophosphatemia in the absence of azotemia. He introduced the concept of glomerulotubular imbalance to explain these manifestations and postulated deficient renal tubular reabsorption of glucose, amino acids, water, calcium and phosphate associated with relatively normal rates of glomerular filtration of these substances.

The first hint of the occurrence of this syndrome in the adult is contained in the report of Milkman[4] in which he describes the roentgen features of osteomalacia with multiple symmetric "fractures" in a forty-two year old woman with renal glycosuria and hypophosphatemia. Ten additional adult cases‡ have since been documented.[5–13] The adult form of the disease differs from the childhood type primarily in its roentgen features. In the former osteomalacia and pseudofractures are evident; in the latter the roentgen characteristics of rickets are predominant. In addition the disease is much more benign in the adult and less refractory to therapy.

The accumulated data, particularly those of McCune, Mason and Clarke[14] in the childhood form of this syndrome, and those of Cooke, Barclay, Govan and Nagley,[9] Linder, Bull and Grayce,[7] Milne, Stanbury and Thomson[5] and Lambert and de Heinzelin de Brancourt[13] in the adult form appear to substantiate Fanconi's original pathogenetic concept, namely, tubular dysfunction without proportional glomerular deficiency. The defects appear to lie primarily in the proximal convoluted tubule, as those functions classically relegated to the distal portion of the nephrons (production of ammonia and acid, and the ability to produce a concentrated urine) are relatively well preserved in a majority of the reported cases.

Other features of note reported in this syndrome are varying degrees of systemic acidosis, ketonuria, proteinuria, manifestations of hypokalemia or hypokalemic-like episodes, occasional abnormal glucose tolerance curves, hyperchloremia and cystinosis; a relatively high familial incidence of related abnormalities and a frequent anamnesis of consanguinity.

The present report is concerned with an adult subject with this syndrome in whom investigations were undertaken to elucidate the nature of the renal defects.

CASE REPORTS

A. B., a fifty-four year old white male grocer, first came under our surveillance in September, 1951, complaining of severe pains in the back, shoulders, ribs and thighs, and severe weakness with inability to walk unassisted. Without previous significant illness, he first noted weight loss, weakness and dull low-back pain in 1944. At that time glycosuria, with a normal fasting blood sugar concentration, and proteinuria were first discovered. In 1945 a diagnosis of osteoarthritis was made and local roentgen therapy

‡ Age thirteen was arbitrarily chosen as the dividing age between childhood and adult cases. Actually, of the twelve documented cases two were aged thirteen and sixteen. The remainder ranged from twenty-nine to fifty-six years when the diagnosis of Fanconi syndrome was first made. The minimum criteria accepted for inclusion into this group were renal glycosuria, hypophosphatemia and roentgenographic abnormalities of bone.

* From the Departments of Medicine and Pediatrics, and the Laboratory Services of The Mount Sinai Hospital, New York, N. Y. Supported by a grant from the American Heart Association.
† Rosenstock Fellow in Medicine.

was prescribed with little success. In 1946 pathologic fractures of the right eighth and ninth ribs were discovered. Malignancy was suspected but extensive investigation failed to substantiate this suspicion. The diagnosis of Fanconi syndrome was first made at the Presbyterian Hospital in New York in 1947. At that time his symptoms were essentially the same as those at the onset. Except for percussion tenderness over the lower dorsal vertebrae, a left indirect inguinal hernia and a moderately enlarged prostate gland, the physical examination was negative. Laboratory investigation revealed renal glycosuria with a normal glucose tolerance curve, low serum inorganic phosphate, elevated serum alkaline phosphatase, hyperchloremic acidosis and hyperaminoaciduria with a normal plasma amino acid concentration. (Table 1, column 1.) Renal plasma flow, determined by Dr. Stanley E. Bradley utilizing renal p-aminohippurate extraction and the Fick principle, was normal (753 cc./min.). Bence-Jones protein was absent from the urine. Bone marrow aspiration was not performed at this time. A diet high in calcium, phosphorus and vitamin D resulted in no substantial improvement.

During the four years prior to the initial admission to Mount Sinai Hospital in 1951 the patient had become completely bedridden. Since 1944 he had lost forty pounds in weight and two inches in height. Physical examination revealed a chronically ill, poorly nourished man whose activity was markedly limited because of severe bone pain. With the support of a cane he could manage a few steps with a waddling gait. His blood pressure was 140/76. There was marked tenderness to percussion over the spine, rib cage and arms. The remainder of the examination revealed no other abnormalities.

Laboratory investigations (Table 1, column 2) indicated the presence of chemical abnormalities qualitatively similar to those present five years previously. Some deterioration of renal function had occurred, as evidenced by a slightly elevated blood urea nitrogen concentration and a markedly depressed phenol red excretion rate. The hyperchloremic acidosis was more marked. The glucose tolerance curve was now diabetic in

TABLE 1
ROUTINE LABORATORY DATA DURING VARIOUS HOSPITALIZATIONS

		1947*	Sept. 1951	Nov. 1951	July 1952	Sept. 1952
Hemoglobin	gm. %	16.0	14.0	12.5	.....	12.5
ESR (Westergren)	mm./hr.	40	67	.....	.....	60
Maximum urine specific gravity		1.012	1.016	.....	1.014	1.015
Proteinuria		3+	1+	1+	1+	3+
Glycosuria		2+	2+	2+	3+	2+
Urine PSP excretion	%/2 hr.	20–25	8.0	0.0	.....	.....
Plasma or serum concentrations						
Urea N	mg. %	10	38	20	17	40
Creatinine	mg. %	.....	3.6	2.4	2.7	4.5
Uric acid	mg. %	.....	1.7	....	2.8	3.5
Inorganic phosphorus	mg. %	1.5–1.9	1.7	2.8	3.9	4.7
Calcium	mg. %	9.6–11.2	9.5	9.2	.....	12.0
Fasting glucose	mg. %	80	96–123	....	120	94
Cholesterol	mg. %	390	337	....	.....	480
Albumin/globulin	gm. %	4.2/3.0	4.5/2.9	....	3.9/3.2	.....
Alkaline phosphatase (King-Armstrong units)		35	41	24	27	23
Sodium	mEq./L.	147†	136	139	140	139
Potassium	mEq./L.	3.7	3.1	5.9	2.7	3.6
Chloride	mEq./L.	112	121	111	116	110
Bicarbonate	mEq./L.	21	16.7	19	18.2	19.4
Blood pH		7.38–7.40	.....	....	7.31	7.33
Amino acids	mg. %	4.5	.....	....	.....	.....
Urine amino acids	mg./24 hr.	1300	.....	....	.....	.....

* The figures in this column were obtained from the records of Presbyterian Hospital, N. Y.
† Indirectly calculated value, not determined.

form, although the fasting blood sugar concentration was normal. (Table II.) The reducing substance in the urine was readily fermented by yeast and characteristic glucosazone crystals appeared following addition of phenylhydrazine to the urine. Qualitative tests for fructose and pentoses were negative. For the first time Bence-Jones proteinuria was repeatedly observed. Bone marrow aspirations from multiple sites yielded marrow containing from 8 to 10 per cent multinucleated plasma cells consistent with a diagnosis of multiple myeloma. Electrophoretic studies of serum proteins revealed an abnormal peak migrating somewhat slower than gamma globulin. (Fig. 1.) Roentgen studies revealed mild generalized decalcification of the skeleton and symmetrical linear zones of decalcification in both scapulas, in the upper shaft of both femoral bones and in the right ninth rib, resembling the pseudofractures described by Milkman.[4] There were no osteolytic lesions. (Fig. 2A.)

TABLE II
RESULTS OF ORAL GLUCOSE TOLERANCE TESTS

		Blood Glucose (mg. %)	
		1947*	1951
Fasting		80	123
Time after test meal (min.)	30	155	298
	60	211	345
	120	160	355
	180	91	270
	240	80	...

* These values obtained from Presbyterian Hospital records.

Following the studies to be described the patient was given a high calcium diet, 50,000 units vitamin D, 3 gm. calcium lactate, 12 gm. sodium bicarbonate and 60 to 120 cc. Shohl's mixture* per day. Ankle edema developed rapidly on this regimen. Potassium bicarbonate, 4 gm. per day, was therefore substituted for the sodium salt. After two months the plasma bicarbonate concentration had risen from 16.7 to 19 mEq./L., the potassium from 3.1 to 5.9 mEq./L., and the chlorides had fallen from 121 to 111 mEq./L. (Table I, column 3.) However, there was no alleviation of bone pain or improvement in the roentgen evidences of osteomalacia. The patient was discharged in January, 1952, and spent the winter in Florida. He was advised to take 160 cc. Shohl's mixture, 50,000 units vitamin D, 3 gm. calcium lactate and 4 gm. potassium bicarbonate per day.

When he was next seen by us in July, 1952, he was markedly improved. He had gained about ten pounds, was completely free of bone pain and able to walk without the slightest difficulty. We were chagrined to learn that he had discontinued all medication except vitamin D and calcium lactate shortly after his discharge from the hospital, and had substituted one quart of fresh orange juice daily and full exposure to the Florida sun. The plasma inorganic phosphorus concentration had risen to 3.9 mg. per cent and the potassium had fallen to 2.7 mEq./L. The plasma sodium and bicarbonate concentration were essentially unchanged. (Table I, column 4.) A bone marrow aspiration yielded 14 per cent plasma cells. Roentgen studies of the skeleton now revealed complete disappearance of the pseudofractures and increased calcium deposition. (Fig. 2B.)

On September 4, 1952, the patient was again admitted for investigation. At this time he complained of mild bone pain and, for the first time, of angina on effort. His physical status was essentially unchanged. However, the laboratory studies revealed considerable deterioration of glomerular function. (Table I, column 5.) Plasma urea, uric acid, creatinine and phosphate concentrations were all significantly elevated above previous figures. Upon completion of the studies the patient returned to Florida. He was given a high carbohydrate, low salt diet. At the time of writing (May, 1953) a report from his physician* in Florida indicated that no essential change had occurred in the patient's physical status since discharge (September, 1952).

SPECIAL INVESTIGATIONS

Renal Clearance Studies. Renal clearance studies were performed during the patient's first admission to Mount Sinai Hospital in 1951, using standardized clearance technics,[15] before any specific therapy was instituted. The results

* Shohl's mixture consisted of 98 gm. of sodium citrate and 140 gm. of citric acid in 1,000 cc. of water.

* We are indebted to Dr. Morton Halpern of Coral Gables, Fla., for keeping us informed of the patient's physical status.

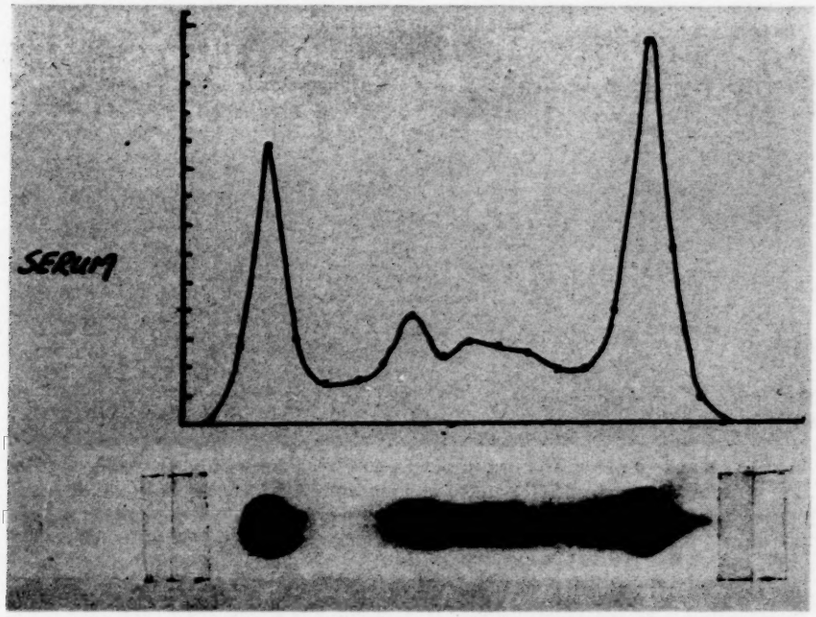

FIG. 1. Electrophoretic pattern of serum revealing an abnormal peak migrating at a slower rate than gamma globulin.

(Table III) indicate a markedly disproportionate reduction in several modalities of proximal tubule activity as compared with glomerular activity. Thus, although the glomerular filtration rate (C_{in} and C_{cr}) was reduced to approximately 32% of expected normal, the clearance of p-aminohippurate (C_{PAH}), the maximum tubular secretory capacity for PAH (Tm_{PAH}) and the maximum tubular reabsorbtive capacity for glucose (Tm_G) were all reduced to approximately 7 per cent of expected normal. The ratios C_{in}/C_{PAH}, C_{in}/Tm_{PAH} and C_{in}/Tm_G express this glomeruloproximal tubular imbalance. We were surprised to find a markedly depressed plasma urate concentration (1.7 mg. per cent) in the presence of a rather severe reduction of glomerular function. An explanation for this seeming anomaly was found in the high urate clearance (40.2 cc./min.), almost five times the normal value, and at the level of glomerular filtration for this subject. For reasons which will be elaborated, we believe this phenomenon to be a result of complete failure of proximal tubular reabsorption of filtered uric acid, another manifestation of glomeruloproximal tubular imbalance.

An inorganic phosphate clearance of 25.7 cc./min. and a C_P/C_{in} ratio of 0.68 are inordinately high for plasma concentrations of phosphate ranging between 1 and 2 mg. per cent. In normal subjects Lambert, Van Kessel and Leplat[16] found phosphate/endogenous creatinine clearance ratios of between 0.01 and 0.12 at serum concentrations between 2 and 4 mg. per cent. Between 1 and 2 mg. per cent the expected normal ratio would be still lower. The high phosphate clearance reflects another manifestation of glomeruloproximal tubular imbalance, since phosphate presumably is reabsorbed by this portion of the nephron.[17] However, this latter manifestation of imbalance is partially reversible as correction of the acidosis results in lower phosphate clearances (*vide infra*).

The routine clearance values for potassium, sodium and chloride are difficult to interpret since the patient was not on a controlled intake of these substances preceding the study. The facts that C_{Na} and C_{Cl} were only 1.54 and 1.31 cc./min., respectively, and that the patient accumulated edema fluid while taking sodium bicarbonate suggest that the proximal tubules were reabsorbing filtered sodium and chloride efficiently, since this part of the nephron normally is responsible for the reabsorption of about 85 per cent of these ions from the glomerular filtrate.[18] Table IV reveals the effect of osmotic diuresis upon the excretion of these substances. During osmotic diuresis induced by glucose during measurement of Tm_G, the amount of filtered sodium and chloride reabsorbed dropped

FIG. 2A. X-ray of pelvis and upper portions of both femoral bones, taken during first Mount Sinai Hospital admission, September, 1951, revealing mild generalized decalcification and symmetric linear zones of "pseudofractures" (arrows).

FIG. 2B. X-ray of pelvis and upper portions of both femoral bones, taken during second Mount Sinai Hospital admission, July, 1952, revealing recalcification.

to 83.7 and 77.1 per cent, respectively, from values of 95.8 and 96.5 per cent. The production of edema during sodium bicarbonate therapy appears to have been more a manifestation of reduced glomerular function than of increased tubular reabsorption of sodium.

A C_K/C_{in} ratio of 0.61 (Table III) is rather high. It is of interest to note that during osmotic diuresis the clearance of potassium rose to that of the inulin clearance (Table IV), suggesting that tubular reabsorption of potassium may have been inhibited to some extent by the osmotic forces.

Effect of Alkalis upon the Acid-base Composition of the Plasma and Urine. The patient was given a specially prepared diet containing 150 gm. carbohydrate, 70 gm. fat, 70 gm. protein and 2 to 3 gm. sodium chloride. After three days on this diet, control twenty-four-hour urine collections were obtained and fasting bloods were drawn daily for three days. These specimens were analyzed for creatinine, pH, sodium, potassium and chloride concentrations and plasma CO_2 content. The effect of several alkalinizing regimens upon endogenous creatinine clearances (C_{cr}), plasma electrolyte concentrations and urine electrolyte output while on this fixed diet is presented on Table V. On a regimen con-

sisting of 60 cc. Shohl's mixture, 3 gm. potassium chloride and 12 gm. sodium bicarbonate daily, the plasma bicarbonate concentration rose from 17.8 mEq./L. to 23.9 mEq./L. After four days there was little change in the plasma sodium, potassium or chloride concentrations. concentrations. Only on one occasion, November 21, was there a significant drop in plasma chloride concentration. The plasma sodium concentration remained relatively constant throughout, ranging from 138 to 142 mEq./L. Alkalinization appeared to have little effect on the

TABLE III
RESULTS OF RENAL CLEARANCE STUDIES*

Renal Clearances		Observed	Expected Normal	Clearance Ratios × 100	Observed	Expected Normal
Inulin (C_{in})	cc./min.	37.7	120	C_{in}/C_{PAH}	86.1	20.0
Endogenous creatinine (C_{cr})	cc./min.	37.6	120	C_{in}/Tm_{PAH}	639	150
p-Amino hippurate (C_{PAH})	cc./min.	43.8	600	C_{PAH}/Tm_{PAH}	742	749
Phosphate (C_P)	cc./min.	25.7	12.0†	C_{in}/Tm_G	143	34.3
Urate (C_{urate})	cc./min.	40.2	8.4	C_P/C_{in}	68.2	10.0
Potassium (C_K)	cc./min.	23.2	var.	C_K/C_{in}	61.5	var.
Sodium (C_{Na})	cc./min.	1.54	var.	C_{urate}/C_{in}	107	7.0
Chloride (C_{Cl})	cc./min.	1.31	var.	C_{Na}/C_{in}	4.09	var.
$Tm_{Glucose}$ (Tm_G)	mg./min.	26.3	350	C_{Cl}/C_{in}	3.48	var.
Tm_{PAH}	mg./min.	5.9	80	.....	.....	.....

* All clearance values represent the average of at least three clearance periods, and are corrected for an ideal surface area of 1.73M².

† Normal value obtained from Lambert, van Kessel and Leplat.[16]

The urine pH rose as high as 7.74 from control values between 6.42 and 6.75. The presence of alkaline urines (pH 7.70–7.74) with plasma bicarbonate levels of 22.6 to 23.9 mEq./L. suggests loss of bicarbonate in the urine (a low "renal threshold" for bicarbonate). Because of rapid weight gain and the development of ankle edema the sodium bicarbonate was discontinued and potassium bicarbonate, 4 gm. per day, was substituted and the Shohl's mixture was increased to 90 cc. per day. After six days on this regimen the plasma potassium concentration rose to 4.50 mEq./L. from previous low values of 3.18 to 3.28 mEq./L. However, the plasma bicarbonate concentration and urine pH dropped somewhat. The Shohl's mixture was therefore increased to 120 cc. per day. This resulted in little further change, except to increase the urine sodium output.

Further attempts to correct the low plasma bicarbonate by increasing alkali administration did not appear warranted in view of the previous development of edema. When alkaline medication was discontinued, there was a prompt fall in urine pH and plasma potassium and bicarbonate

twenty-four-hour endogenous creatinine clearance, which remained remarkably constant between 17.2 and 22.1 cc./min. (uncorrected for surface area). The blood pH during the control period averaged 7.32. On November 15, after receiving 12 gm. sodium bicarbonate per day for five days, the blood pH rose to 7.44. The plasma inorganic phosphate concentration rose from control values of 1.7 and 1.8 mg. per cent to 2.8 mg. per cent.

Investigations of the Renal Aberrations Concerned with Acid-base Regulation. Effects of varying degrees of systemic acidosis upon the renal clearances of potassium, phosphate and bicarbonate: The renal clearances of inulin, potassium and inorganic phosphate were determined during a control period; after three days of alkali therapy, consisting of 60 cc. Shohl's mixture and 12 gm. sodium bicarbonate daily; and again after receiving 4 gm. ammonium chloride daily for three days. In addition, the renal clearance of bicarbonate was determined during the control period and after the period of ammonium chloride administration. For these latter clearances urine was collected by means of an indwelling

catheter which drained under mineral oil. Air and distilled water bladder washes were not used, urine collection errors being minimized by thirty-minute urine collections and manual compression of the bladder. The results are presented in Table VI. All clearance values represent the mean of three clearance periods. There appears to be a direct correlation between the degree of acidosis and the renal clearances of potassium and inorganic phosphate: the more marked the systematic acidosis, the higher the clearance ratios C_K/C_{in} and C_P/C_{in}. During the period of ammonium chloride administration C_K was actually greater than C_{in}, demonstrating the presence of tubular secretion of potassium. The hyperphosphaturia and hyperkaluria were considerably enhanced by systemic acidosis. The presence of significant bicarbonate clearances during marked systemic acidosis indicates a distinct defect in bicarbonate reabsorption, as one would not ordinarily have expected any bicarbonate in the urine even during the control periods. Pitts et al. have demonstrated that bicarbonate does not normally appear in the urine unless plasma concentrations greater than 24 mEq./L. are present.[19]

TABLE IV

EFFECT OF OSMOTIC DIURESIS DURING DETERMINATION OF T_{mG} UPON THE TUBULAR REABSORPTION OF SODIUM, POTASSIUM AND CHLORIDE

	Control	Osmotic Diuresis
Filtered Load μEq./min.		
Sodium	4480	6253
Potassium	109	128
Chloride	3720	4970
Excreted in Urine μEq./min.		
Sodium	189	1022
Potassium	67	127
Chloride	130	1139
Tubular Reabsorption μEq./min.		
Sodium	4291	5231
Potassium*	....	....
Chloride	3590	3831
Per Cent of Load Reabsorbed		
Sodium	95.8	83.7
Potassium*	....	....
Chloride	96.5	77.1
Clearance Ratios × 100		
Sodium/inulin	4.1	16.3
Potassium/inulin	61.5	99.2
Chloride/inulin	3.5	22.9

* These values for potassium would be meaningless since a sizable but unknown moiety of excreted potassium is known to be secreted by the tubules.

Effects of the administration of phosphate buffer upon bicarbonate reabsorption and the renal production of hydrogen and ammonium ions: Latner and Burnard[20] succeeded in reducing urinary bicarbonate excretion and in increasing renal production of hydrogen and ammonium by means of intravenous phosphate infusions in infant subjects with idiopathic hyperchloremic tubular acidosis. Since our patient presented similar aberrations in acid-base balance (hyperchloremic acidosis with relatively alkaline urine and excess urinary bicarbonate) we thought it might be of some interest to determine the effects of phosphate infusion upon these manifestations.

In order to establish a maximum stimulus for ammonium and hydrogen ion production by the kidney, ammonium chloride was administered in a dose of 4 gm. per day for three days. On the fourth day the renal clearances of inulin, PAH, sodium, potassium, phosphate, bicarbonate and chloride, and the excretion of ammonium and hydrogen ions were determined. Following three twenty-to-thirty minute control periods isotonic sodium phosphate at a pH of 7.4 was infused at a rate of 7 cc./min. (1.44 μmol./min.) and the effect of the increasing filtered loads of phosphate upon the foregoing functions were determined. All urine samples were again collected under oil to prevent escape of CO_2. The partial pressures of CO_2 in blood and urine were calculated from the total CO_2 content. Urine titratable acidity was determined immediately following urine

TABLE V

EFFECTS OF VARIOUS THERAPEUTIC REGIMENS UPON URINE AND PLASMA ELECTROLYTE CONTENT

Date	24 Hr. C_{cr}	Urine pH	24 Hr. Output in Urine			Plasma Concentration				Inorganic Phosphate
			Sodium	Potassium	Chloride	Sodium	Potassium	Chloride	Bicarbonate	
	cc./min.	pH	mEq.	mEq.	mEq.	mEq./L.	mEq./L.	mEq./L.	mEq./L.	mg. %
10/29	Special diet started—C_{150}, P_{70}, F_{70}, containing 2–3 gm. salt									
11/2	18.1	6.75	41.2	57.2	58.9	140	3.18	118	16.0	1.8
11/3	20.2	6.63	50.4	63.7	54.3	...	....	....	....	...
11/6	19.2	6.42	55.2	86.8	56.2	139	3.20	119	17.8	1.7
11/11	Shohl's mixture—60 cc., KCl 3 gm., $NaHCO_3$ 12 gm., vitamin D 50,000 U, calcium lactate 3 gm.									
11/14	22.1	7.70	162	82.4	56.2	141	3.18	117	23.9	...
11/15	18.6	7.74	186	76.2	64.5	138	3.28	118	22.6	...
11/16	Shohl's mixture increased to 90 cc., $KHCO_3$ 4 gm. substituted for $NaHCO_3$									
11/21	21.5	7.46	52.1	132	66.6	139	3.40	110	20.0	2.8
11/22	19.4	7.32	54.1	93.5	44.0	142	4.50	116	19.8	...
11/26	Shohl's mixture increased to 120 cc.									
12/4	17.2	7.14	94.1	105	49.2	140	4.10	118	19.4	...
12/5	19.8	7.16	85.2	97.5	69.0	142	3.33	119	20.8	...
12/6	All medication but vitamin D and calcium lactate discontinued									
12/7	19.4	7.02	70.4	82.5	64.0	140	3.20	119	16.4	...
12/8	21.4	6.94	67.6	79.6	52.5	138	3.26	118	17.2	...

TABLE VI*

EFFECT OF VARYING DEGREES OF ACIDOSIS UPON POTASSIUM, PHOSPHATE AND BICARBONATE CLEARANCES

	Plasma		Renal Clearance Values				Clearance Ratios × 100		
	Bicarbonate	pH	Inulin	Potassium	Phosphate	Bicarbonate	C_K/C_{in}	C_P/C_{in}	C_{HCO_3}/C_{in}
	mEq./L.		cc./min.	cc./min.	cc./min.	cc./min.			
Control	17.3	7.36	26.1	16.8	21.2	1.71	64.4	81.2	6.56
Alkalies	22.6	7.40	23.5	12.2	10.4	....	52.0	44.3	....
Ammonium chloride	12.3	7.33	22.3	25.9	20.6	0.69	117	93.0	3.09

* All clearance values represent the average of at least three clearance periods.

collection. The detailed results of this study are presented in Table VII.

Ammonium chloride administration resulted in a plasma bicarbonate concentration of 12.3 mEq./L. and a blood pH of 7.33. The phosphate infusion produced an increase in the load of inorganic phosphate delivered to the proximal tubules to a maximum of 96 μmol./min. from a control value of 28.3 μmol./min. This resulted in an increase in the urinary titratable acidity, no change in ammonia output or urine pp_{CO_2}, and an increase in bicarbonate excretion, rather than a decrease as found by Latner and Burnard.

If a correction factor for loss of renal mass is applied (as indicated by the depression in glomerular filtration rate), the resulting production of ammonia and titratable acidity by the kidneys of our patient during the ammonium chloride-induced acidosis would still be far below normal. Thus the corrected values for ammonia and acid production are 24 and 65 μEq./min., respectively, as compared with the values reported by Pitts et al.[21] of about 60 and 160 μEq./min., respectively, in normal subjects with comparable degrees of ammonium chloride-induced acidosis.

Since excessive quantities of bicarbonate were present in the urine in spite of markedly reduced plasma bicarbonate concentrations, defective reabsorption of this anion must have occurred. A major fraction of the bicarbonate filtered at the glomerulus appears to be reabsorbed by the tubules as an integral part of the mechanism responsible for the tubular secretion of acid.[22] Since the renal tubular capacity for acid production was impaired in our patient the excessive quantities of urinary bicarbonate may be explained on this basis. However, the occurrence of increased bicarbonate excretion during phosphate loading, in spite of an increment in titratable acidity, suggests an alternative mechanism, namely, that a significant fraction of bicarbonate reabsorption may occur in a manner unrelated to hydrogen ion formation. Thus phosphate loading would impose an osmotic or competitive stress on this process, resulting in an increase in bicarbonate excretion. The presence of large quantities of phosphate buffer results in an increment in titratable acidity. The increment in bicarbonate reabsorption which occurs as an integral part of the increased acid secretion would thus be masked by the bicarbonate diuresis resulting from inhibition of that portion of bicarbonate reabsorption which is unrelated to acid production. The presence of

TABLE VII

EFFECT OF PHOSPHATE INFUSION UPON THE ELECTROLYTE PATTERN AND ACID-BASE COMPOSITION OF THE PLASMA AND URINE

Period	Plasma								Blood pH	Urine										
												Excretion								
	Sodium	Potassium	Chloride	Bicarbonate	Inorganic Phosphate	Calcium	PP_{CO_2}		C_{In}	pH	PP_{CO_2}	Sodium	Potassium	Chloride	Bicarbonate	Inorganic Phosphate	H^+	NH_4^+
	mEq./L.	mEq./L.	mEq./L.	mEq./L.	mM/L.	mg./100 cc.	mm. Hg	pH	cc./min.	pH	mm. Hg	μEq./min.	μEq./min.	μEq./min.	μEq./min.	μmol./min.	μEq./min.	μEq./min.
U_1	125	3.63	114	12.3	1.27	12.2	29.9	7.33	22.3	6.21	58.6	71.2	94.2	105	6.81	47.7	23.4	7.68
U_2	...	....	...	....	.....	....	....	....	23.0	6.31	53.6	73.0	95.2	114	8.86	48.0	22.0	8.39
U_3	126	3.50	115	12.4	1.31	12.4	29.9	7.33	21.5	6.35	52.5	85.2	87.0	118	9.82	47.0	21.1	9.28
	Isotonic Na_2PO_4 at pH 7.4 infused at 7 cc./min. (1.44 μmol./min.)																	
U_4	128	3.45	114	12.8	2.65	11.1	33.2	7.32	14.8	6.47	49.5	80.9	61.9	85.4	10.1	63.2	24.0	5.58
U_5	...	....	...	....	....	....	....	....	16.5	6.50	52.2	121	75.6	98.1	12.2	112	29.7	4.20
U_6	128	3.42	113	13.2	4.52	....	33.2	....	15.7	6.58	56.8	141	72.1	105	16.0	134	34.5	3.63
U_7	...	....	...	....	....	....	....	....	18.6	6.61	59.9	222	87.8	139	21.2	169	40.4	4.95
U_8	129	3.40	114	12.2	5.38	9.9	29.9	7.35	17.8	6.68	57.0	246	92.8	184	26.0	191	43.3	6.24

other severe tubular reabsorptive defects in this syndrome lends some weight to this concept.

We found the partial pressures of CO_2 in the urine of our subject to be considerably greater than in his plasma. The plasma CO_2 partial pressure (pp_{CO_2}) ranged from 29.9 to 33.3 mm. Hg, whereas in the urines it ranged from 49.5 to 59.9 mm. Hg. Latner and Burnard, utilizing the concepts of Pitts et al.,[19] interpreted the high pp_{CO_2} in the urine of their subjects with tubular acidosis as indicative of distal tubule production of acid. In this view the acid produced by the tubule cells reacts with bicarbonate in the tubule liberating CO_2 which does not have enough time to attain equilibrium pressures with blood and so passes into the bladder urine at a high pp_{CO_2}. However, in accordance with the recent investigations of Kennedy, Orloff and Berliner concerning the significance of the CO_2 tension of the urine,[23] we favor a different interpretation of the high urine pp_{CO_2} in our subject. In this view acid urine from a minority of intact nephrons mixes with alkaline urine from a majority of malfunctioning nephrons resulting in the liberation of CO_2. This mixing occurs in the renal calyceal system where opportunity for CO_2 equilibration with blood must be considerably less than in the tubules. The resulting bladder urine would thus have a pp_{CO_2} in excess of that of blood.

The low serum potassium concentration is presumably the result of excessive urinary losses of this cation as part of the renal mechanism for sparing sodium. Excessive urinary potassium loss may be produced experimentally by reducing renal acid production during systemic acidosis by means of carbonic anhydrase inhibition.[24] The resulting potassium diuresis is presumably the result of increased tubule secretion of this ion *pari passu* with decreased hydrogen ion secretion, sodium being spared in cationic exchange with potassium instead of hydrogen across the tubule cells. The poor acid production by the kidneys of our subject suggests that this mechanism plays a significant role in the production of the observed hypokalemia. However, deficient reabsorption of filtered potassium may be of some importance in this disease, since osmotic diuresis resulted in a marked increase in urinary potassium output.

Renal Clearance of Glucose. Glucose clearances averaged 14.6 cc./min. at a plasma glucose concentration of 106 mg. per cent, yielding a C_G/C_{in} ratio of 0.56. Instead of the normal reabsorption of 100 per cent of the filtered glucose, only 44 per cent was reabsorbed. The filtered load of glucose was only 27.7 mg./min. The rate of glucose reabsorption was 12.2 mg./min., 55 per cent of the patient's maximum reabsorptive capacity (Tm_G), indicating very severe impairment of this proximal tubular function. This marked glomerulotubular imbalance results in varying losses of glucose via the urine at all physiologic ranges of plasma glucose concentration. The constant loss of considerable quantities of glucose (20 to 30 gm./day) may explain the change in the glucose tolerance curve in our patient from a normal pattern to a diabetic one over a four-year observation period. The persistent threat of hypoglycemia must be met by increased rates of gluconeogenesis and glycogenolysis or perhaps decreased rates of glucose utilization. Abnormal glucose tolerance curves have been reported in other subjects with this syndrome.[3]

Amino Acid Metabolism. In 1947 hyperaminoaciduria in the presence of normal plasma amino acid concentrations was established in this patient at the Presbyterian Hospital. The twenty-four-hour excretion of these acids amounted to 1,300 mg., the normal being between 200 and 400 mg. Chromatographic analysis of the urine was performed by Dr. Charles E. Dent. He found large amounts of serine, glycine, alanine, glutamine and valine; moderate amounts of cystine, taurine, threonine, citrulline, histidine, arginine, lysine, and leucine; and traces of proline, phenylalanine, tyrosine and glutamic acid. He reported, "There is no question of there being an amino-aciduria with amino acid distribution of the Fanconi type. The urine is similar to the three I have examined in England but there are a few important differences. The A.B. urine has much more cystine (enough to pass as a "cystinuria" if the other amino acids were not found). It has lysine and arginine in equal amounts and there is no evidence of seryl-glycyl-glycine. All three of the previous cases had a cirrhosis of the liver."

Since Pitts has demonstrated that the amino acid reabsorptive processes of the renal tubules are distinct from those of glucose reabsorption,[25] the amino-aciduria present in our subject must represent a reabsorptive defect independent from that producing glycosuria. By means of competition experiments, Beyer et al.[26] have indicated that at least three separate types of transport systems are present in the dog for tubular reabsorption of different amino acids. Thus the system involved in the transport of glycine differs

from that involving leucine and isoleucine, and arginine, histidine and lysine constitute a group of their own in this regard. Since the urine of our patient contained significant quantities of amino acids in each of these three groups it may be reasoned that all three of the requisite transport systems were involved. In addition, our subject had an unusual amount of cystine in his urine. This has been reported previously with the Fanconi syndrome[13] and when not associated with cystinosis may be considered to be simply one facet of the generalized amino-aciduria.

Calcium and Phosphorus Metabolism. On a low calcium diet containing 100 mg. calcium and 500 mg. inorganic phosphorus per day the urinary excretion of calcium was 185 mg. per day in 1947 and 50 mg. per day in 1951. He excreted 590 mg. of phosphorus per day in 1947 and 927 mg. in 1951. The hyperphosphaturia was persistent. We believe this to be primarily the result of a specific renal reabsorptive defect for phosphate. That acidosis influences the magnitude of this defect is indicated by our studies. With severe ammonium chloride-induced acidosis the phosphate clearance was at the level of the glomerular filtration rate indicating complete absence of phosphate reabsorption. With partial correction of the acidosis the phosphate clearances were lowered, although they remained significantly greater than normal. That the high phosphate clearance in this syndrome is not primarily due to secondary hyperparathyroidism, the mechanism invoked by Albright and Reifenstein,[27] is indicated by two well documented cases[9,13] in which marked hyperphosphaturia was present without systemic acidosis. Thus the proposed sequence: acidosis → calcium mobilization and loss in urine → tendency to hypocalcemia → hyperparathyroidism → hyperphosphaturia is impossible in these cases.

Osteomalacia in the Fanconi syndrome appears to be primarily the result of constant urinary loss of inorganic phosphate with consequent hypophosphatemia. Hypercalcuria in our patient, as in other reported cases, is relatively mild and inconstant. Thus nephrocalcinosis and nephrolithiasis have never been reported in the Fanconi syndrome. The symmetric pseudofractures are probably the result of the pressure of pulsating arteries on softened bone.[28]

Urate Clearance. Since urate clearances in this subject were found to be markedly elevated in spite of a depressed plasma urate concentration it was postulated that the specific tubular defects of the Fanconi syndrome encompassed those systems responsible for reabsorption of filtered urate. In view of the demonstration of complete ultrafiltrability of plasma urate by Yü and Gutman,[29] the approximate identity of urate and inulin clearances could be satisfactorily explained by assuming complete failure of the urate reabsorptive process. It was decided to test this hypothesis by determining the effect of benemid® (p-[di-n-propylsulfamyl]-benzoic acid) upon the C_{urate}/C_{in} ratios in this subject. This drug has been shown by Beyer et al.[30] to be a potent inhibitor of p-amino hippurate, penicillin and phenol red secretion, and by Sirota, Yü and Gutman[31] to be a strong inhibitor of urate reabsorption by the renal tubules, functions presumably resident in the proximal convolutions. The oral administration of 2 gm. of benemid to the present subject produced no significant change in the C_{urate}/C_{in} ratio, the value remaining close to unity. (Table VIII.) With similarly conducted experiments the drug has invariably resulted in a significant rise in the C_{urate}/C_{in} ratio in gouty subjects,[31] normal persons and subjects with moderate renal insufficiency.[32] There is nothing to suggest that the tubule transport system responsible for urate reabsorption has anything in common with glucose or amino acid transport except for the requisite energy requirements. Thus benemid, while normally inhibiting urate transport, has no effect whatsoever upon glucose or amino acid transport.[30]

It is of interest that Milne, Stanbury and Thomson[5] report a blood urate concentration of only 1.5 mg. per cent in their adult subject with the Fanconi syndrome. The inulin clearance in their patient was 31 cc./min., close to the value obtained in our subject. They did not determine urate clearances but do mention the presence of increased output of uric acid following oral glycine administration.

Exogenous Creatinine Clearances. The intravenous administration of creatinine in man normally results in creatinine clearances which are about 30 per cent higher than simultaneous glomerular filtration rates.[33] Crawford[34] was able to reduce exogenous creatinine/inulin clearance ratios by loading the proximal tubules with diodrast or p-amino hippurate, suggesting that this portion of the nephron is responsible for the secretion of exogenous creatinine. Accordingly, creatinine was infused into our patient

intravenously and the C_{cr}/C_{in} ratios determined for endogenous creatinine during control periods and for exogenous creatinine during the infusion of creatinine. As indicated in Table VIII the clearance of exogenous creatinine did not differ significantly from that of endogenous creatinine or inulin, and benemid failed to affect these clearances. These results suggest that the secretion of exogenous creatinine which would ordinarily occur was absent in this subject with the Fanconi syndrome.

TABLE VIII*

EFFECTS OF BENEMID UPON THE RENAL CLEARANCES OF EXOGENOUS CREATININE AND URATE

	Renal Clearances			Clearance Ratios	
	Inulin	Creatinine	Urate	× 100	
	cc./min.	cc./min.	cc./min.	C_{urate}/C_{in}	C_{cr}/C_{in}
Control Period	26.1	27.8	25.7	98.5	107
Exogenous creatinine	27.5	24.8†	27.1	98.6	90.2
Following benemid	25.6	27.2†	27.5	107	106

* Each set of values represent the mean of at least three clearance periods.

† These values represent exogenous creatinine clearances. The value during the control period is the endogenous creatinine clearance.

Progression of the Renal Lesion. Several aspects of renal function had been followed for a period of five years. Comparison of the values indicates gradual deterioration of the modalities studied. In 1947 his glomerular filtration rate was 55.7 cc./min./1.73M^2; in September, 1951, it had fallen to 31.1 and one year later to 26.5 cc./min./1.73M^2. The maximum reabsorptive capacity for glucose, Tm_G, was 50.9 mg./min./1.73M^2 in 1947; in 1951 this value was 26.3. The ability to form ammonium ions under maximum ammonium chloride-induced acidosis fell from 34.6 mEq./day in 1947 to 11.1 in 1952. The urine pH in 1947 could be lowered to 5.0; in 1951 the lowest attainable value was 6.2. The clearance of p-amino hippurate fell from 43.8 to 26.5 cc./min./1.73M^2 over a one-year period from 1951 to 1952.

The gradual depression of glomerular filtration over the years reflected itself in increasing plasma concentrations of urea, creatinine, uric acid and inorganic phosphate. (Table I.)

Preservation of the acid- and ammonia-producing functions of the kidney has frequently been described* but follow-up studies of the duration of the present report have not been previously recorded. Depression of these functions in our subject may represent either the natural course of the disease or the result of renal damage resulting from the coincidental development of multiple myeloma.

Analytic Methods Utilized in the Preceding Investigations. Inulin: Schreiner;[36] p-amino hippurate: Smith et al.;[37] creatinine: Bonsnes and Taussky;[38] calcium: Kramer and Tisdall;[39] inorganic phosphate: Fiske and SubbaRow;[40] sodium and potassium: flame photometer, Perkin-Elmer model 120 A; chloride: van Slyke and Hiller;[41] pH of blood and urine: Cambridge pH meter with glass electrode; ammonia and urea: Van Slyke and Cullen;[42] uric acid: Buchanan, Bloch and Christman;[43] urine titratable acidity: Pitts and Alexander;[44] glucose: Nelson;[45] carbon dioxide: Van Slyke and Sendroy;[46] bicarbonate: calculated from carbon dioxide content and pH using Henderson-Hasselbach equation.

DISCUSSION

The Fanconi syndrome is apparently the result of an inherited defect.[41] In the adult form

* Ammonia and acid production have been classically relegated solely to the distal tubules on the basis of the micropuncture studies of Montgomery and Pierce in the amphibian kidney.[35] This concept may have to be modified in mammals on the basis of recent indirect studies of Berliner et al.[22,24]

of the disease Stowers and Dent[8] conclude that transmission is by means of a dominant gene which is not sex-linked. However, the possibility that an acquired renal lesion may produce the adult form of the syndrome cannot be definitely excluded. Only two of the twelve reported adult cases have definite familial histories of rickets and glycosuria.[7,8] The family history of our patient was completely negative for all symptoms or diseases which might be related to the syndrome. The presence of Bence-Jones proteinuria, atypical bone marrow plasmacytosis and a slow moving plasma protein component in the electrophoretic pattern suggest the possibility that multiple myeloma may have been the predisposing factor for development of the Fanconi syndrome in our case. However, we favor the view that the two diseases are coincidental since neither Bence-Jones proteinuria nor any other indication of multiple myeloma was present in 1947, when all the clinical and laboratory characteristics of the Fanconi syndrome were manifest. We are aware of no cases of "myeloma kidneys" in which any of the manifestations of the Fanconi syndrome have been reported. In a series of ninety-seven cases of multiple myeloma observed by Snapper, Turner and Moscovitz[47] the prime manifestations of renal involvement were proteinuria, azotemia and fixation of specific gravity. Renal glycosuria was never noted.

In this syndrome the concurrence of so many reabsorptive and secretory abnormalities, all thought to be resident in the proximal tubule, suggests the possibility of a non-specific common denominative defect, perhaps one which involves an energy source such as phosphate bond energy. The demonstrated absence of intracellular alkaline phosphatase in the proximal tubules of subjects dying with the Fanconi syndrome[8,9] may be related to this defect.

The treatment of this disease should aim at correction of the systemic acidosis, the osteomalacia and the hypokalemia. We were able to accomplish only partial correction of the acidosis in our patient. The sodium intake necessary for full correction resulted in fluid retention and edema formation, presumably an indirect result of decreased glomerular function. Hypokalemia was successfully treated by means of potassium salts. Osteomalacia and bone pain did not appear to respond to vitamin D and supplementary calcium administration. The subsequent disappearance of these latter manifestations of the syndrome might be a sequel of phosphate retention resulting from progressive decrease in glomerular function. In view of the demonstrated urinary loss of large quantities of inorganic phosphate the oral administration of supplementary phosphate salts appears indicated. Lambert and de Heinzelin de Brancourt[13] report excellent results in the treatment of the osteomalacia of their adult subject with the Fanconi syndrome by means of oral calcium phosphate.

SUMMARY AND CONCLUSIONS

1. The twelfth recorded case of Fanconi syndrome in an adult is reported. Symptoms referable to this disease were first manifested at the age of forty-five, nine years prior to the time of reporting. The course was complicated by the development of multiple myeloma, thought to be etiologically unrelated to the Fanconi syndrome.

2. The principal renal abnormalities present were the result of marked glomerulotubular imbalances. The tubular reabsorptive defects were characterized by renal glycosuria, depressed Tm_G, amino-aciduria, hyperuricosuria, hyperphosphaturia, excessive urinary bicarbonate losses in spite of systemic acidosis, and possibly by hyperkaluria. The secretory defects were characterized by inability to secrete exogenous creatinine and by marked depressions of C_{PAH}, Tm_{PAH} and the capacity for phenol red excretion. The depressions of these tubular functions were significantly greater than concomitant decreases in glomerular filtration.

3. The renal abnormalities were associated with hyperchloremic acidosis, hypophosphatemia, hypokalemia, elevated serum alkaline phosphatase activity and the development of a diabetic type of glucose tolerance curve. The systemic acidosis appeared to be the result of the following contributory factors: (a) poor renal production of acid and ammonia resulting in urinary bicarbonate loss; (b) continued urinary loss of amino acids requiring fixed base for excretion; (c) a possible defect in bicarbonate reabsorption unrelated to acid production; (d) abnormal glucose metabolism resulting in the production of ketone bodies requiring fixed base for excretion. The hyperchloremia may represent a compensatory increase in tubular reabsorption of chloride to balance the excessive bicarbonate loss. The hypophosphatemia is the result of a primary tubular reabsorptive defect for this anion and a

secondary effect of acidosis, both resulting in a constant loss of inorganic phosphate in the urine. The hypokalemia appears to be the result of increased urinary losses resulting from increased tubular secretion of potassium and a possible primary reabsorptive defect for potassium.

4. The presenting clinical manifestations of the syndrome were weakness, severe bone pain and osteomalacia with pseudofractures. The weakness appeared to be related to excessive potassium loss and the osteomalacia to constant inorganic phosphate and inconstant calcium losses in the urine.

5. Therapy should aim at correction of the systemic acidosis and replenishment of the urinary losses of potassium, phosphorus and calcium. In this patient attempts to correct the acidosis resulted in edema formation. The osteomalacia and bone pains were refractory to vitamin D and supplementary calcium administration. Later improvement in these manifestations are thought to be the result of phosphate retention incident to decreasing glomerular activity.

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Plasma Thromboplastin Component Deficiency*

I. Studies on Its Inheritance and Therapy

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A SYNDROME clinically resembling hemophilia but due to a hemostatic defect correctible on *in vitro* testing by hemophilic plasma has been reported by Aggeler et al.[1,2] Mixtures of plasma from their patient and patients with hemophilia showed mutual correction of the coagulation defect in each condition, a fact indicative of a separate and distinct deficiency. While the corrective ability of hemophilic plasma on the clotting defect of the patient was strong evidence against true hemophilia, Aggeler demonstrated by additional laboratory tests a clear differentiation between the two conditions. Thus both barium sulfate–adsorbed plasma and Cohn's Fraction I, each capable of correcting the defect in hemophilia, were totally ineffective in the newly described syndrome, whereas serum, ineffective in hemophilia, was markedly active in corrective ability. The factor lacking in this condition has been called plasma thromboplastin component and the syndrome resulting from its absence, plasma thromboplastin component (PTC) deficiency.

Independently, Schulman and Smith[3] in this country and Biggs et al.[4] in England have described similar cases. In their report on a family with yet another hemophilia-like disorder, plasma thromboplastin antecedent deficiency, Rosenthal, Dreskin and Rosenthal[5] presented incidental data in a case identical with that of Aggeler. Most recently three cases showing all the laboratory criteria of the new condition as described by Aggeler were reported by Lewis and Ferguson.[6]

In the original case of PTC deficiency a family history of hemorrhagic diathesis was lacking, giving no clue as to the genetic background of this condition. Although the next two cases reported in this country lacked any familial history, the fact that all the patients were males was strong presumptive evidence for a mode of inheritance not unlike that of hemophilia. In the series of Biggs and her co-workers[4] this suspicion was confirmed since four of the seven cases had family histories identical with that of hemophilia. In addition, they noted that the carrier state in the female did show some stigmas, in that impaired prothrombin consumption was noted in some of the clinically unaffected female carriers. A similar mode of inheritance was noted in two of the three cases described by Lewis and Ferguson although detailed studies on the families were not presented.

The present report is concerned with studies on a case of plasma thromboplastin component deficiency presenting a definite family history. In addition, therapeutic trials of various types of plasma are presented and the usefulness of ordinary stored plasma in PTC deficiency is indicated.

CASE REPORT

R. F. (M.S.H., No. 3822), a fifteen year old white male, was admitted to the hospital for the third time in February, 1953, because of pain in the left elbow and wrist of sixteen hours' duration. Ever since birth a tendency toward easy bruising had been noted by the patient's family. When the patient was nine months old, various hemorrhagic episodes prompted the family to conduct a searching investigation for a similar tendency in other members of the family. No member on the paternal side of the family was known to have any hemorrhagic tendency. Since, with the exception of the mother, the maternal family all resided in Sweden, aid was

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sought through the appropriate consular service. Medical documents then revealed that four male children of a maternal grandaunt had died of a hemorrhagic disease considered to be hemophilia. One other male sibling from this union was unaffected, as was a female child, the offspring of a second maternal grandaunt. Both maternal grandparents were supposedly normal.

Because of this history the patient was considered to have classical hemophilia. Over the years numerous hemarthroses, hemorrhages into the skin and muscles, hematuria, melena and on one occasion hematemesis necessitated over sixty hospital admissions. The coagulation time was always prolonged being over four hours on occasion, and the serum prothrombin activity was consistently elevated. Prompt correction of the hemostatic defect could always be brought about by fresh plasma or blood and its frequent use resulted in a surprising lack of permanent joint involvement.

Physical examination on the present admission revealed a well nourished although small-statured boy in considerable distress from a swollen, painful left elbow, which he kept in an elevated guarded position and partially flexed. Other findings were also confined to the joints, the right elbow being somewhat tender and extensible only to about 140 degrees. Both ankles were minimally swollen but non-tender.

Laboratory examination revealed slight anemia, a prolonged coagulation time, normal bleeding time and high serum prothrombin activity.

The administration of 250 cc. of type-specific frozen fresh plasma resulted in prompt cessation of pain and quick resorption of the hemarthrosis.

Six days following the last administration of plasma blood was drawn from the patient for use in matching experiments with another patient with hemophilia. Mutual correction of the hemostatic defect in each case prompted further investigation of the patient.

Methods and Materials. All blood was collected carefully by the two-syringe technic.[7] Initially, uncoated syringes were used but the majority of specimens was obtained with silicone-coated needles and syringes (dri-film) and transferred to silicone-coated or uncoated pyrex tubes as required. Plasma was obtained from blood mixed with one-tenth volume 0.1 M sodium oxalate in silicone-treated tubes and centrifuged at 2000 R.P.M. for ten minutes. Plasma not used immediately was stored at minus 30°C. for future work. Coagulation times were measured by a modified Lee-White method at 37°C. using 1 ml. amounts of blood placed into pyrex tubes with internal diameter of 11 mm. One or two tubes were used depending on the procedure. Bleeding time was determined by the method of Duke. The prothrombin activity of undiluted plasma and plasma diluted with nine volumes of barium sulfate-adsorbed normal plasma* was measured by the one-stage method of Quick.[8] Serum prothrombin activity one hour after clotting was measured by the method of Stefanini and Crosby,[9] thrombin formation being halted by the addition of one-tenth volume of 0.1 M sodium oxalate to the serum. Normal values for this method in our laboratory were twenty-one seconds or greater, equivalent to 12 per cent or less serum prothrombin activity. Labile factor activity was determined by the method of Stefanini[10] and concentration determined from a standard curve. Fibrinogen was determined by the biuret reaction.[11]

Recalcification time of mixtures of the patient's plasma with normal and abnormal plasmas was performed at 37°C. in the proportions indicated in Table II. Hemophilic plasma I was verified against a proved case of antihemophilic globulin deficiency† and confirmed by the lack of corrective effect of serum and the corrective effect of barium sulfate-adsorbed plasma, and antihemophilic globulin. Hemophilic plasma II and III were authenticated in a similar manner. The plasma labelled PTC I was obtained from Dr. Schulman‡ while the plasma labelled PTC II was obtained from a three year old male whose plasma was shown to lack this factor. Plasma from a patient with the newly described plasma thromboplastin antecedent deficiency[5] (PTA deficiency), a hemophilia-like disease, is also included.

Whole blood–plasma mixtures were performed by the addition of 1 ml. of whole blood of the patient to 0.1 ml. of the plasma to be tested. The mixture was incubated at 37°C. and the effect on coagulation time and serum prothrombin activity (exactly one hour after clotting) noted. In each series of such tests a

* Fifty milligrams of $BaSO_4$ C.P. (Baker) per milliliter of plasma at 22°C. for ten minutes.

† We are indebted to Dr. R. Rosenthal for providing a reference plasma used in his study and demonstrated to be a "true" hemophilic.

‡ We are indebted to Dr. I. Schulman for providing plasma from the patient described by him.[3]

blank of whole blood plus 0.1 ml. of normal saline was used as control. The addition of substances other than plasma or different amounts of the substances added to the whole blood of the patient is indicated in Table III.

The thromboplastin generation test was performed by the method of Biggs and Douglas,[12,13] using serum of the patient, barium sulfate–adsorbed normal plasma and a saline suspension of normal platelets.

The *in vivo* effect of various plasmas, serum or antihemophilic globulin was measured by a two-tube coagulation time, and serum prothrombin activity drawn at one-hour, six-hour, one-day, three-day and seven-day intervals after completion of the intravenous administration of the substance being tested. Preliminary to each trial of test substances a two-tube coagulation time and serum prothrombin activity were determined. Although periods of observation longer than a week seemed at times justified clinically, an effort was made to keep the serum prothrombin activity a bit lowered (about fourteen seconds) in view of the severe nature of the patient's hemorrhagic manifestations.

Family studies consisted of history, two-tube coagulation time, serum prothrombin activity, plasma prothrombin activity (undiluted and 10 per cent dilution with barium sulfate–adsorbed plasma) and determination of the corrective effect of the 0.1 ml. of plasma against 1 ml. of the patient's whole blood.

Results. Routine studies of the various coagulation factors of the patient are presented in Table I. For comparison, similar studies on a patient with "true" hemophilia and a normal are presented. A marked similarity between the patient under study and the "true" hemophiliac is evident, both having prolongation of the whole blood coagulation time, prolongation of the plasma recalcification time and high serum prothrombin activity. The amount of serum prothrombin conversion accelerator in the patient's spontaneously clotted blood was deficient but was normal when thromboplastin was added to the whole blood. Similar findings have been reported in true hemophiliacs.[14] From the studies presented in Table I it is not possible to distinguish between the patient with plasma thromboplastin component deficiency and the true hemophiliac.

The effect on the recalcification time of mixtures of normal and abnormal plasmas with the patient's plasma in varying proportions is presented in Table II. Mutual correction of the coagulation defect was shown by mixtures of the patient's plasma with the plasma from all the hemophilic patients and the patient with plasma thromboplastin antecedent deficiency. As might

TABLE I

COMPARISON OF COAGULATION PROFILE OF PATIENT, HEMOPHILIAC AND NORMAL PATIENT

Determination	Patient	Hemophiliac	Normal
Two-tube coagulation time	32 min.	30 min.	9 min.
Recalcification time, plasma	540 sec.	560 sec.	120 sec.
Prothrombin activity, undiluted plasma	12.0 sec.	12.0 sec.	12.0 sec.
Prothrombin activity, 10% plasma	24.2 sec.	25.0 sec.	24.0 sec.
Serum prothrombin activity	12.8 sec.	13.0 sec.	26.0 sec.
S.P.C.A.	37%	64%	70%
S.P.C.A. with thromboplastin added	93%	.....	.....
Labile factor	14.0 sec.	.....	14.4 sec.
Fibrinogen	335 mg. %	.....	300 mg. %
Fibrinolysis (24 hr.)	Negative	Negative	Negative
Platelet count (direct)	320,000/mm.^{3}	280,000/mm.^{3}	250,000/mm.^{3}
Bleeding time (Duke)	2 min.	.....	2 min.

TABLE II

RECALCIFICATION OF MIXTURES OF PATIENT'S PLASMA WITH NORMAL AND ABNORMAL PLASMAS

Plasma of patient (ml.)	0	.05	.10	.15	.20
Test plasma (ml.)	.20	.15	.10	.15	0
$CaCl_2$ .02M (ml.)	.20	.20	.20	.20	.20
Normal	2′	2′10″	2′10″	2′10″	6′53″
Hemophilic I	12′	3′35″	3′15″	3′30″	9′
Hemophilic II	9′	3′40″	....	3′20″	7′20″
Hemophilic III	9′15″	3′45″	3′35″	3′20″	10′15″
PTA	4′	2′5″	2′5″	2′5″	6′
PTC I	25′	12′35″	9′30″	7′25″	7′10″
PTC II	10′	9′45″	9′	9′	8′30″

be expected, normal plasma corrected the deficiency in the patient under study and, furthermore, mixtures of the patient's plasma with normal plasma even in high proportion failed to prolong the recalcification time of the normal, ruling out any circulating anticoagulant. In contrast, the patient's plasma when mixed with the plasma of other patients with plasma thromboplastin component deficiency showed no mutual correction, increasing proportions merely reducing the recalcification time toward the time of the less severe defect. The mixtures of hemophilic plasma with the patient's plasma while showing a marked mutual corrective effect always had a slightly prolonged recalcification time. Since rigid control of the number of platelets was impossible in this study because of the necessity of using frozen specimens, the exact significance of this observation must await further work. However, the possibility of multiple deficiencies in the thromboplastin complex of varying severity must be considered.

TABLE III
EFFECT ON SERUM PROTHROMBIN ACTIVITY OF THE ADDITION OF ONE-TENTH VOLUMES OF VARIOUS PLASMAS AND FRACTIONS

Serum Prothrombin Activity (sec.)	Fractions Added to 1 ml. of Patient's Blood	Serum Prothrombin Activity (sec.)
Before	Effective Fractions	After
13.6	0.1 ml. normal plasma	28.8
13.6	0.1 ml. normal serum	125.0
14.6	0.1 ml. hemophilic plasma	27.0
13.6	0.1 ml. PTA plasma	51.0
14.2	0.1 ml. normal plasma, 7 days at 4°C.	24.6
12.8	0.1 ml. normal plasma, 14 days at 4°C.	24.8
14.6	0.1 ml. normal plasma, 19 days at 4°C.	28.2
14.6	0.1 ml. normal plasma, fresh frozen	23.0
13.6	0.05 ml. rabbit brain thromboplastin	22.4
	Non-effective Fractions	
12.4	0.1 ml. normal saline	12.4
12.4	0.1 ml. $BaSO_4$ absorbed normal plasma	12.4
14.4	0.1 ml. PTC plasma	14.2
13.8	0.1 ml. 0.05 % antihemophilic globulin	13.8
13.8	0.1 ml. 0.005% antihemophilic globulin	14.2
13.8	0.1 ml. 0.0005% antihemophilic globulin	14.0
14.4	0.1 ml. lyophilized plasma	16.0
13.6	0.05 ml. rabbit brain thromboplastin heated 60°C. for 30 min.	13.4

The ability of various plasmas, serum and plasma fractions to correct the impaired serum prothrombin consumption of the patient's whole blood is shown in Table III. Similar to the effect on recalcification time, plasma from a patient with true hemophilia and plasma from the case of plasma thromboplastin antecedent deficiency produced normal serum prothrombin consumption. Particularly good consumption was brought about by the addition of small amounts of serum, a finding noted by Lewis and Ferguson[6] with respect to freshly prepared serum fractions. Of especial note was the corrective ability of plasma stored at 4°C. for periods as long as nineteen days, indicating marked stability of the deficient component when stored in this fashion. This is in contrast to the known lability of antihemophilic globulin and Factor v (labile factor), but parallels the stability of prothrombin and serum prothrombin conversion accelerator. Those preparations which had little or no corrective ability included barium sulfate–adsorbed plasma, antihemophilic globulin, lyophilized plasma (Lyovac R) and heated rabbit brain thromboplastin.

The *in vitro* corrective ability of plasma stored in a fashion similar to ordinary refrigerated banked blood prompted further investigation as to the therapeutic efficacy of such stored plasma when administered *in vivo*. In addition, the therapeutic effect of hemophilic plasma and citrated normal serum was also tested because of similar good results during *in vitro* trials. Figures 1 and 2 demonstrate that when given in equivalent amounts, frozen fresh plasma stored in the deep freeze, seven day old plasma stored at 4°C., seven day old citrated serum stored at 4°C. and even hemophilic plasma stored in a like fashion have about equal therapeutic effect. Although the effect as measured by the clotting time persisted for about one week for the plasmas and even longer for serum, the effect on restoration of serum prothrombin consumption toward normal was largely dissipated by seventy-two hours. This occurred even when a larger amount of plasma was given. Clinically, in this patient at least, no hemorrhagic manifestations were encountered until the two-tube coagulation time was over twenty minutes even though serum prothrombin activity was high for several days before this figure was reached. Since this patient was young and had a good vascular system, a similar finding might not be encountered in an older person whose local hemostatic mechanisms are impaired. The total ineffectiveness of a potent antihemophilic globulin preparation to correct the deficiency in the patient contrasted strikingly with the effect of various unfractionated plasmas. A similar lack

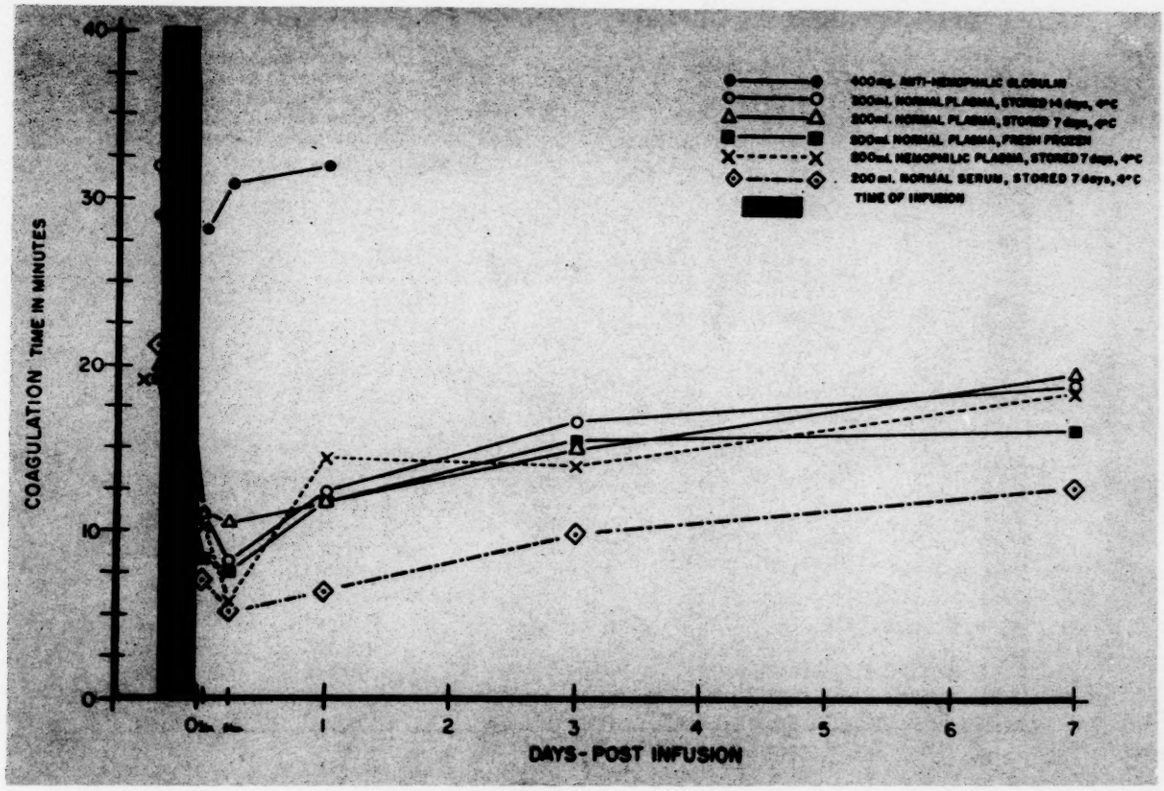

FIG. 1. Effect of infusion of various plasmas, serum and antihemophilic globulin on the coagulation time. The latter was ineffective whereas serum and all plasmas were corrective. Note seemingly enhanced correction of serum.

of plasma thromboplastin component in Fraction I has been shown by Aggeler.[1,2]

Results of the thromboplastin generation test of Biggs and Douglas[12,13] using the serum component as the variable is graphically indicated in Figure 3. The peak of thromboplastin formation in the patient was delayed and never achieved the levels seen in the normal.

Investigation of the family was limited since members on the maternal side were in Sweden with the exception of the mother. It is noteworthy that the only relative to give a history of any disturbance in hemostasis was the mother. She had noted spontaneous ecchymoses for many years and during numerous operative procedures for fibrous dysplasia of the head of the femur had been known to be a "bleeder." Serum prothrombin consumption in this subject was borderline and the ability of her plasma to correct the defect in her son was poorer than any other relative so tested, although it brought the prothrombin consumption to within normal limits. Reconstruction of the family through history and laboratory tests on the subjects investigated is indicated in Table IV and Figure 4. The mode of inheritance was identical with that of true hemophilia in that transmission was through essentially asymptomatic female carriers, the disease appearing in its overt form in the males who inherited the defective gene. Although recessive in character, some expression of the gene did occur in the female carrier, especially during periods of blood loss.

COMMENTS

The demonstration of a disease clinically identical with hemophilia but differing in the plasma factor which is lacking has presented many new problems. Replacement therapy with the most specific plasma fraction of antihemophilic globulin available today, namely, Fraction I, is totally without effect in plasma thromboplastin component deficiency. In addition to reliance upon it being dangerous to the patient with PTC deficiency, human assay of this material on presumed hemophiliacs is now complicated by this new disease since a preparation may be judged impotent when assayed on a patient with thromboplastin component de-

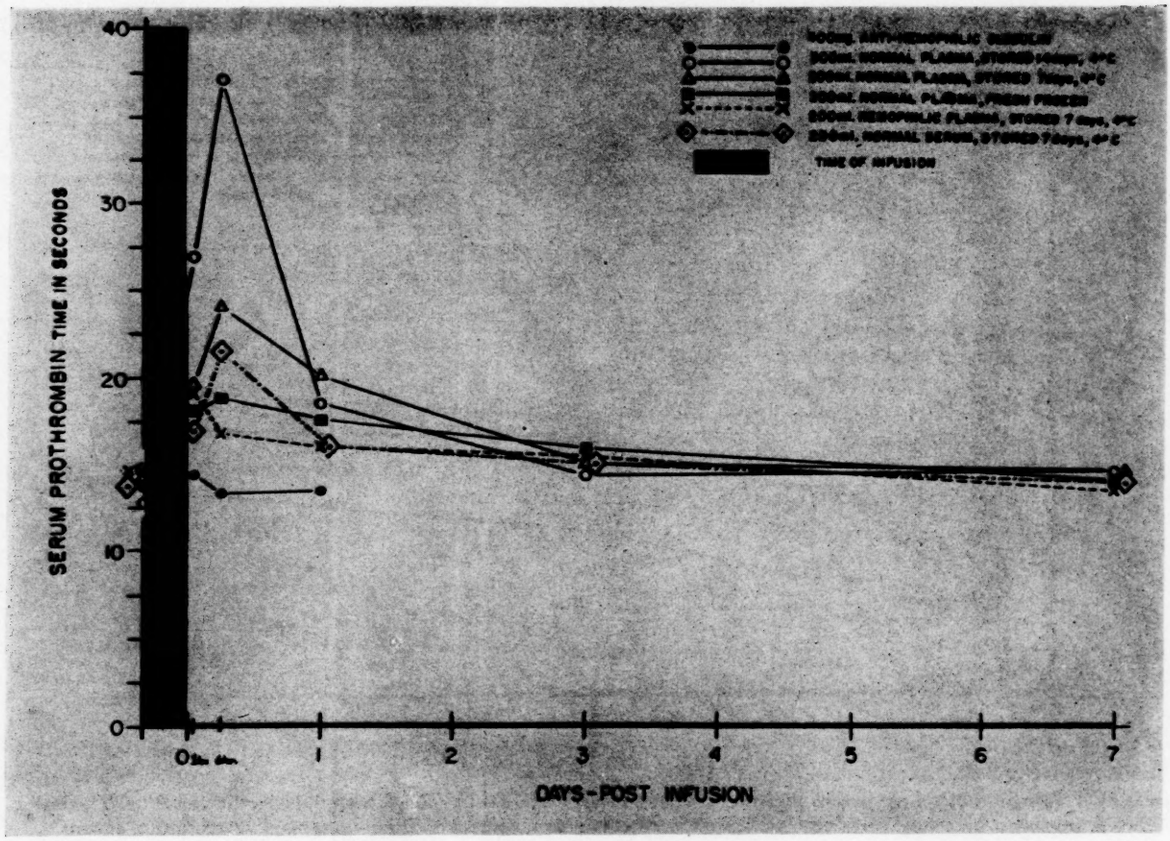

FIG. 2. Effect of infusions of various plasmas, serum and antihemophilic globulin on serum prothrombin activity. Note that the fractions which correct do so for only seventy-two hours.

ficiency. It is therefore important that every case of supposed hemophilia be revaluated and the specific deficiency revealed. Fortunately, the application of plasma-matching mixtures and plasma–whole blood mixtures, as well as testing for the effectiveness of barium sulfate–adsorbed plasma, serum and aged plasma, offers numerous laboratory approaches to such identification. Such screening of hemophiliacs is vastly facilitated once authenticated plasmas are on hand as test substances. Utilizing a combination of the technics presented in the study of the patient described, we have established the diagnosis of plasma thromboplastin component deficiency in five of twenty allegedly classical cases of hemophilia.

Screening and positive identification of the specific defect, besides being of considerable theoretic importance, has practical value. Because of the lability of antihemophilic globulin in ordinary banked plasma or blood, such products when used for hemophiliacs must be freshly obtained or else frozen fresh plasma used. These products are not always available and considerable time can elapse before suitable plasma or blood is obtained. The demonstration that plasma thromboplastin component is stable enables the use of conventionally banked plasma or blood in such cases, taking a considerable amount of strain off the blood-banking installations servicing such patients. Although the exact frequency of plasma thromboplastin component deficiency is not known, our own experience as well as others[4,6] indicates that it is probably not a very rare condition.

The corrective effect of plasma in such cases appears to last for a somewhat longer period than in hemophilia, the therapeutic effect lasting for at least one week. Although *in vitro* studies indicated a possible superiority in the corrective ability of serum as against plasma on a volume for volume basis, comparative *in vivo* trial of such a substance did not confirm this. As measured by the effect on the patient's serum prothrombin activity, citrated normal serum proved to be as effective (but no more so) as an equivalent

amount of plasma. When the coagulation time was used as a criterion for correction, serum showed an enhanced potency in shortening the time of this test. However, this effect cannot be attributed solely to the heightened specific replacement of plasma thromboplastin component by serum, since it was not accompanied by a parallel improvement in serum prothrombin consumption. Moreover it has been noted by us that serum, containing no antihemophilic globulin, can shorten the coagulation time in hemophilia with no corresponding change in the defective consumption of prothrombin. At least a portion of the effect of serum on the coagulation time in plasma thromboplastin component deficiency then seems to be non-specific. Most likely this phenomenon is related to the elaboration of serum prothrombin conversion accelerator from the inert plasma precursor during processing of the serum. Clinically no particular benefit seemed to be derived from the shortened clotting time since ecchymoses appeared after the administration of serum at a time corresponding to the expected appearance after plasma administration.

A mode of inheritance virtually identical with that of true hemophilia is now known in PTC deficiency. Somewhat unusual was the finding of a borderline deficiency of this substance in the mother of the patient together with a clinical history of unexplained, prolonged bleeding during the immediate postoperative period. Female carriers of hemophilia allegedly show no abnormality in coagulation factors, the gene being completely recessive, but the recent finding of Graham, McLendon and Brinkhous[15] of a reduced concentration of antihemophilic globulin in asymptomatic female carriers in families with mild hemophilia is at variance with this view and indicates some expression of a recessive gene. The mother of the patient described may well show a similar expression of a different type of defective gene, a frank hemorrhagic tendency developing only when the concentration of the factor is lowered below the critical level during periods of operative blood loss. Such a mechanism has been postulated by Graham et al. as a possible cause for hemorrhage in mild hemophilia.

TABLE IV

STUDIES ON HEMORRHAGIC TENDENCY IN FAMILY OF PATIENT

Initials, Age, Relationship	Hemorrhagic History	Coagulation Time		Plasma Prothrombin Activity		Serum Prothrombin Activity	S.P.A. of Mixtures Plasma and 1 cc. Patient's Whole Blood
		Tube 1	Tube 2	Undil.	Dil.		
L. F., 39, Mother	Spontaneous ecchymoses, bleeding postoperatively	7′30″	11′30″	11.2″	24.8″	21.2″	23.5″
G. F., 44, Father	None	8′	10′30″	12.0″	24.8″	26.0″	38.2″
W. F., 31, Paternal uncle	None	6′	8′30″	13.2″	30.2″	38.4″	35.0″
H. F., 33, Paternal uncle	None	6′	9′40″	12.0″	22.8″	34.0″	36.4″
S. C., 36, Paternal aunt	None	6′15″	8′30″	12.8″	24.4″	36.2″	28.0″
J. P., 38, Paternal aunt	None	6′30″	10′	12.2″	23.2″	45.0″	41.0″
R. L., 46, Paternal aunt	None	7′30″	10′30″	12.8″	30.8″	26.4″	29.2″
R. F., 15, Patient	Severe	15′	19′	12.0″	24.0″	14.0″	15.4″

Although the exact role of plasma thromboplastin component in the coagulation scheme is not yet well delineated, the recent work of Biggs et al. using a technic for the measurement of human thromboplastin evolution clearly indicates the essential nature of plasma thromboplastin component for thromboplastin formation. Deficiency of this component produces a lag in the formation of thromboplastin, a fact which accounts for the prolongation of the coagulation time of whole blood and recalcified plasma. In addition to this delay in the appearance of thromboplastin, a decrease in the total amount formed is manifest, this fact being indirectly reflected in the poor conversion of

prothrombin to thrombin. These two defects, namely delay in production and poor yield of thromboplastin, can also be demonstrated in true hemophilia, indicative of the closely associated roles of plasma thromboplastin component and antihemophilic globulin. However, in its state in the plasma, plasma thromboplastin component shows more of a similarity to serum prothrombin conversion accelerator than to antihemophilic globulin although the two are quite distinct functionally. Unlike the factor deficient in true hemophilia, plasma thromboplastin component is found in serum, indeed at times appearing to have enhanced activity after blood has clotted. Plasma thromboplastin component is readily removed from plasma by barium sulfate together with prothrombin and serum prothrombin conversion accelerator while no such removal of antihemophilic globulin is possible. The demonstration of normal amounts of serum prothrombin conversion accelerator in patients with plasma thromboplastin component deficiency, especially after the addition of thromboplastin, is clear evidence for the separate identity of each of these coagulation factors.

Recently some controversy has arisen concerning the proper name that should be given to the syndrome arising as a result of plasma thromboplastin component deficiency. Although it has been suggested that such a syndrome be called hemophilia followed by a distinctive letter or number to distinguish it from classical hemophilia,[16] such a classification leaves the way open to errors in therapy. The common practice of calling specially prepared Fraction I, antihemophilic globulin, would create real difficulty since this preparation has no potency whatsoever in plasma thromboplastin component deficiency.

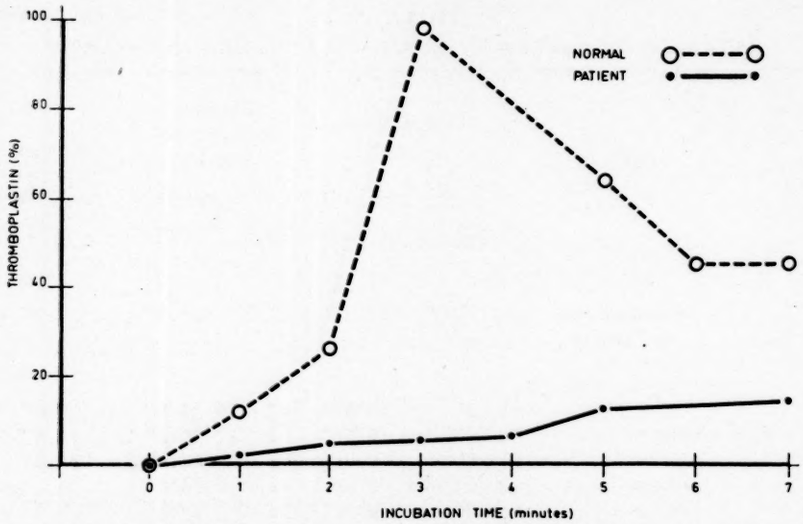

FIG. 3. Thromboplastin generation test. The substitution of the patient's serum for normal serum in the reaction mixture resulted in diminished thromboplastin production.

A more rational approach would be to abandon completely the term hemophilia and substitute a terminology indicative of the specific factor lacking in each case, i.e., antihemophilic globulin deficiency, plasma thromboplastin component deficiency, etc. This has special merit when one regards the confusing terms associated with hemophilia such as pseudohemophilia, parahemophilia and hemophilia-like diseases (circulating anticoagulants). Although the proposed designations are perhaps wordy and lack historical flavor, in common practice the use of initials as abbreviations is practical and in line with recent trends in terminology within the field of coagulation. In the event of any more definitive information concerning the specific role of these factors and their genetic interrelationships, such terms could readily be modified.

SUMMARY

1. A case is presented of plasma thromboplastin component deficiency in a fifteen year old male, clinically resembling true hemophilia (antihemophilic globulin deficiency). Routine coagulation studies differed in no way from that of classical hemophilia.

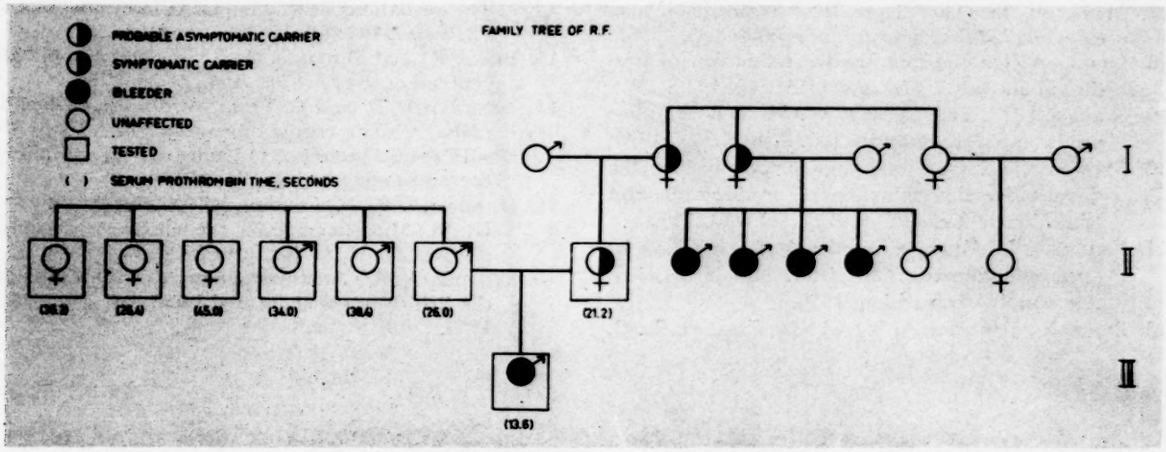

FIG. 4. Mode of inheritance of plasma thromboplastin component deficiency. Transmission is identical to that of hemophilia. Occasional carriers may be symptomatic.

2. Mixtures of the patient's plasma with that of true hemophilic plasma, and plasma from a patient with plasma thromboplastin antecendent deficiency upon recalcification showed mutual correction. No such correction was evident with plasma from two other cases of plasma thromboplastin component deficiency.

3. Hemophilic plasma, PTA deficient plasma, normal plasma, normal serum and normal plasma stored at 4°C. for periods as long as nineteen days could correct the coagulation defect of the patient *in vitro*. Barium sulfate–adsorbed plasma, antihemophilic globulin and plasma from other patients with plasma thromboplastin component deficiency were lacking in corrective effect.

4. Therapeutic trials with frozen fresh normal plasma, normal plasma stored at 4°C. for seven days and fourteen days, citrated normal serum stored at 4°C. for seven days and even hemophilic plasma stored for seven days at 4°C. indicated the effectiveness of these preparations. Although the serum prothrombin activity became quite high seventy-two hours after administration of such plasmas, clinical disease did not appear for at least one week after administration. Antihemophilic globulin had no therapeutic or laboratory effect, restricting its use to cases of true hemophilia only.

5. A family history of hemorrhagic disturbance on the maternal side was elicited, the disease appearing exclusively in males in its overt form. The carrier state in the female was essentially asymptomatic except in the patient's mother where spontaneous ecchymoses and postoperative bleeding appeared. Serum prothrombin consumption in the mother was borderline and her ability to correct the defect in her son was poorer than other relatives although the correction did occur.

6. The need for routine identification of the specific deficiency in each patient now suspected of hemophilia is stressed, especially as a prerequisite to a rational approach to therapy. A terminology based upon such identification is proposed and should do much to dispell the confusion surrounding the use of the term hemophilia in many related and non-related coagulation disturbances.

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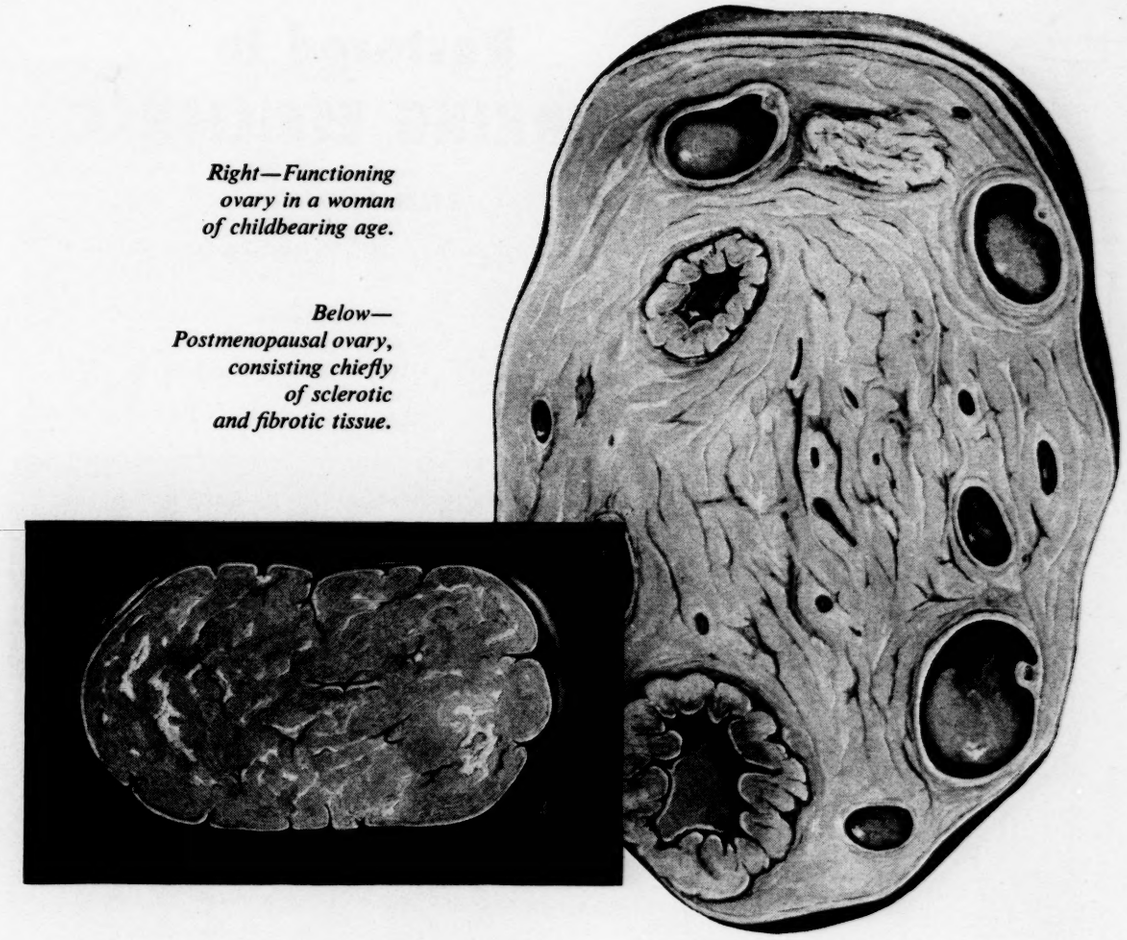

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[1]Sturnick, M. I., and Gargill, S. L.: Clinical Assay of a New Synthetic Estrogen: Vallestril, New England J. Med. *247*:829 (Nov. 27) 1952.

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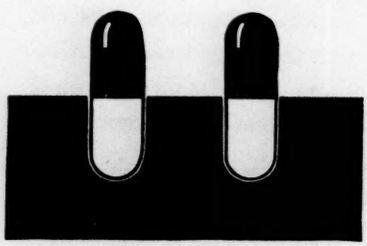

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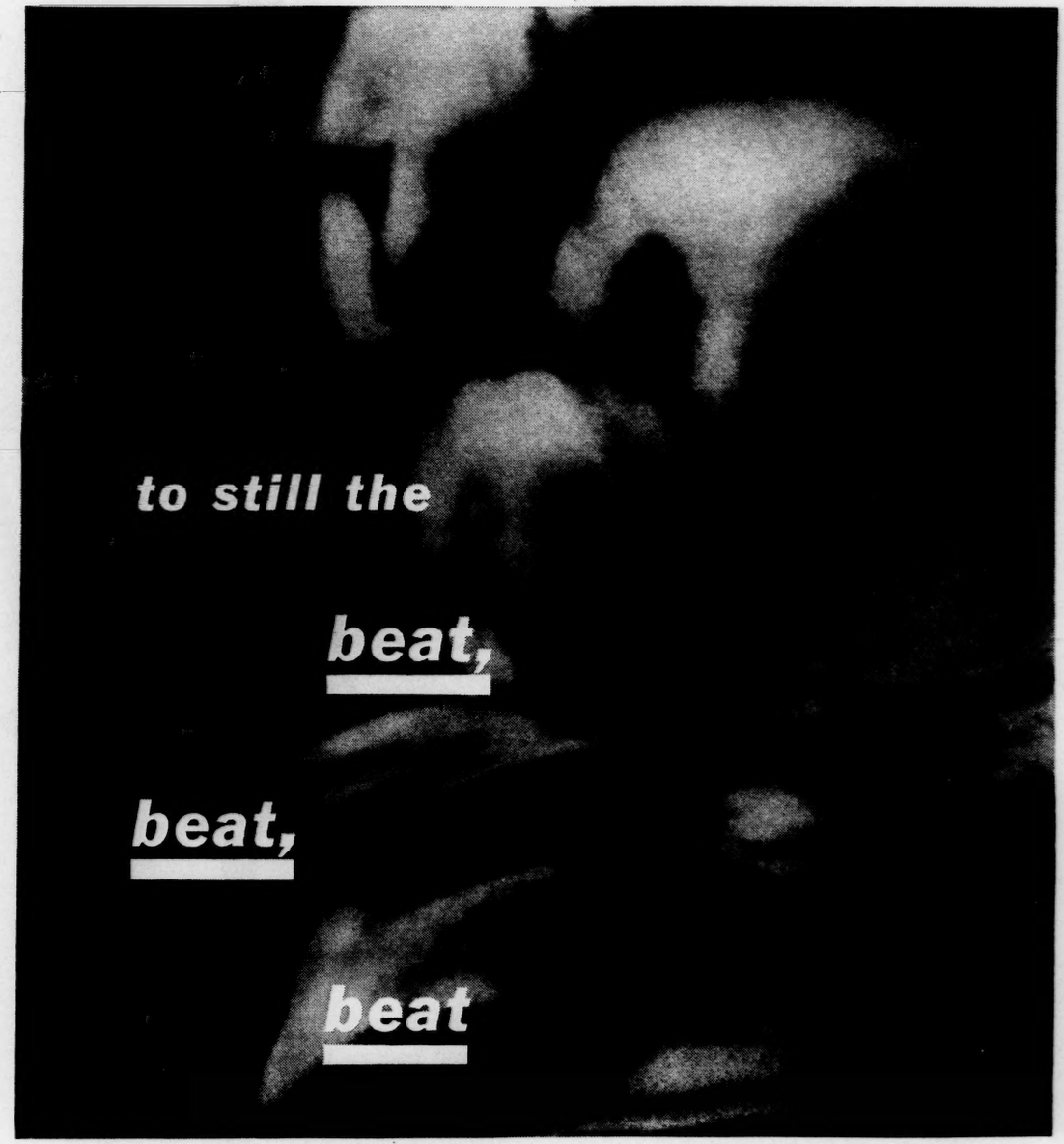

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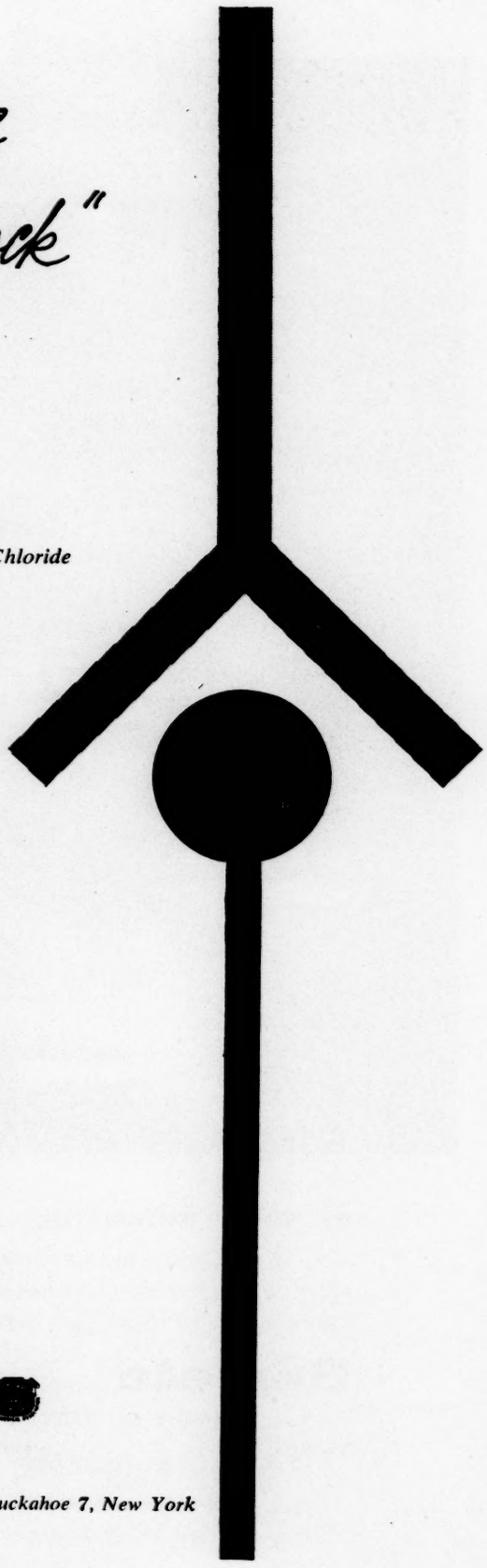

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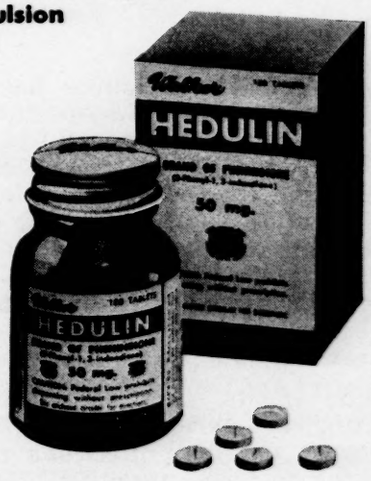

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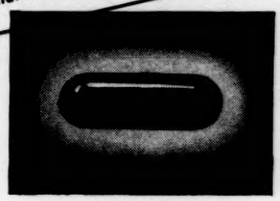

THERE IS NO *SAFER* PREPARATION FOR THE TREATMENT OF HYPERTENSION

Veratrite® brings your hypertensive patients the best therapeutic benefits of Veratrum, since it provides Cryptenamine * the newly isolated, broader safety-ratio Veratrum alkaloid developed through Irwin-Neisler research.

Sustained control of blood pressure, with minimum side reactions and maximum safety, is the significant contribution of Veratrite to the long-term management of hypertension.

Each tabule contains:

Whole-powdered Veratrum viride (*containing Cryptenamine*) . . . 40 C.S.R.† Units

Sodium Nitrite . . . . 1 grain

Phenobarbital . . . . ¼ grain

Carotid Sinus Reflex

Supplied: *Bottles of 100, 500, 1000.*

Veratrite

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

for specific and potent
antiarthritic action

BUTAZOLIDIN®

(brand of phenylbutazone)

BUTAZOLIDIN relieves pain and improves function in the great majority of arthritic patients. Its broad therapeutic spectrum makes it valuable in virtually all the more serious forms of arthritis. *Like other powerful antiarthritic agents,* BUTAZOLIDIN *should be prescribed according to a controlled regimen, based on careful selection of cases, judicious manipulation of dosage, and regular observation of the patient.* To obtain optimal therapeutic results with minimal incidence of side reactions, physicians are urged to send for the brochure "Essential Clinical Data on Butazolidin."

BUTAZOLIDIN® (brand of phenylbutazone) tablets of 100 mg.

(1) Burns, J. J., and others: J. Pharmacol. & Exper. Therap. *106*:375, 1952. (2) Byron, C. S., and Cronstein, H. B.: New York State J. Med. *53*:676 (Mar. 15) 1953. (3) Currie, J. P.: Lancet *2*:15 (July 5) 1952. (4) Davies, H. R.; Barter, R. W.; Coe, A., and Hirson, C.: Brit. M. J. *2*:1392 (Dec. 27) 1952. (5) Delfel, N. E., and Griffin, A. C.: Stanford M. Bull. *2*:65, 1953. (6) Domenjoz, R.: Federation Proc. *11*:339, 1952. (7) Domenjoz, R.: Internat. Rec. Med. *165*:467, 1952. (8) Goldfain, E.: J. Oklahoma M. A. *46*:27, 1953. (9) Gutman, A. B., and Yü, T. F.: Am. J. Med. *13*:744, 1952. (10) Kuzell, W. C.: Annual Review of Medicine, Stanford, Annual Reviews, *3*:367, 1951. (11) Kuzell, W. C., and Schaffarzick, R. W.: Bull. on Rheumatic Diseases *3*:23, 1952. (12) Kuzell, W. C.; Schaffarzick, R. W.; Brown, B., and Mankle, E. A.: J.A.M.A. *149*:729 (June 21) 1952. (13) Kuzell, W. C., and Schaffarzick, R. W.: California Med. *77*:319, 1952. (14) Patterson, R. M.; Benson, J. F., and Schoenberg, P. L.: U. S. Armed Forces M. J. *4*:109, 1953. (15) Rowe, A., Jr.; Tufft, R. W.; Mechanick, P. G., and Rowe, A. H.: Am. Pract. & Digest Treat., in press. (16) Smith, C. H., and Kunz, H. C.: J. M. Soc. New Jersey *49*:306, 1952. (17) Steinbrocker, O., and others: J.A.M.A. *150*:1087 (Nov. 15) 1952. (18) Stephens, C. A. L., Jr., and others: J.A.M.A. *150*:1084 (Nov. 15) 1952. (19) Wilkinson, E. L., and Brown, H.: Am. J. M. Sc. *225*:153, 1953.

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GEIGY PHARMACEUTICALS
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220 Church Street, New York 13, N. Y.
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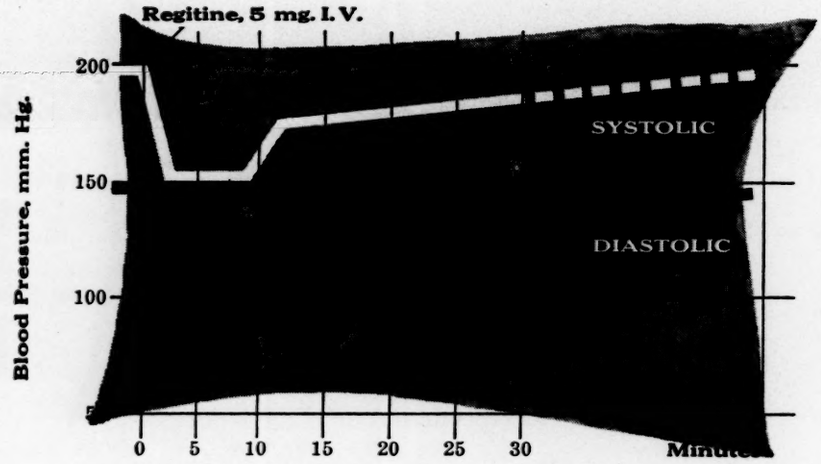
PHEOCHROMOCYTOMA

causes

one curable form of hypertension



Regitine®

the preferred diagnostic agent

Because of its specificity, this potent adrenergic blocking agent affords an eminently safe, accurate, and simple test for the diagnosis of the hypertension-producing tumor – pheochromocytoma.

When it is left untreated, pheochromocytoma is a progressive and eventually fatal condition. After diagnosis, surgical removal of the tumor effects a complete cure. Therefore, "careful consideration of the possible presence of a pheochromocytoma in every patient with hypertension must now be regarded as a diagnostic obligation."[1] Testing is quickly and simply done with Regitine.

The above chart is a schematic representation of the type of response that you can anticipate in the adult hypertensive patient who does have a pheochromocytoma.

For complete information contact your Ciba Professional Service Representative or write to the Medical Service Division.

REGITINE methanesulfonate (phentolamine methanesulfonate Ciba)
REGITINE hydrochloride (phentolamine hydrochloride Ciba)

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Ciba Pharmaceutical Products, Inc., Summit, New Jersey

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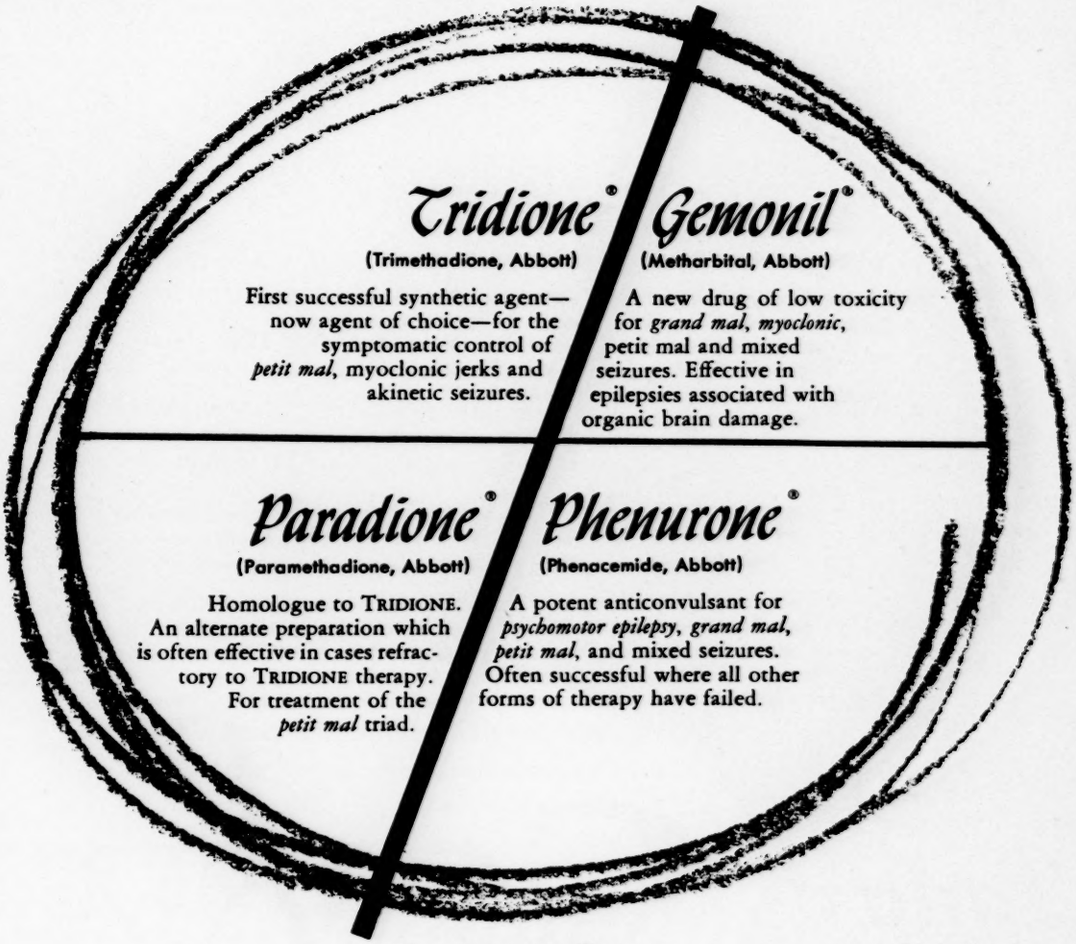

WHY *Four* DRUGS FOR EPILEPSY?

REMEMBER when bromides were the first and last resource of antiepileptic medicine? Hope and doubt were never too far apart. Today you may *choose* your weapon, add or alternate drugs, *individualize* your treatment. Above are four modern anticonvulsants, eminently useful in a variety of seizure types. Each has specific uses, advantages. All are abundantly documented. Remember them. Use them, wisely and carefully. But—please—before you prescribe any of these drugs, write for literature.

1-32A-54

Abbott Laboratories, North Chicago, Illinois. Abbott

Cortril

brand of ***hydrocortisone***

CORTRIL ACETATE TOPICAL OINTMENT

CORTRIL ACETATE OPHTHALMIC OINTMENT

CORTRIL ACETATE AQUEOUS SUSPENSION

With the introduction of CORTRIL Topical Ointment, CORTRIL Ophthalmic Ointment, and CORTRIL Aqueous Suspension for intra-articular injection, significant and definite *anti-inflammatory* action is now possible at the local level *without systemic effect.*

in a wide variety of dermatoses

CORTRIL Topical Ointment, applied locally, is effective in allergic skin disorders. The unique topical action of this corticoid agent safely controls local edema, erythema, and inflammatory infiltration, and markedly relieves the distressing pruritic manifestations of atopic and contact dermatoses.

the anti-inflammatory hormone

in ocular disorders

With CORTRIL Ophthalmic Ointment, local inflammatory edema is safely controlled and fibrous tissue proliferation and corneal vascularization which can result in scarring are significantly inhibited in conditions of the anterior chamber of the eye.

inflamed joints, sprains, and bursitis

Injected directly into arthritic joints and bursae, CORTRIL Aqueous Suspension provides a prompt and striking decrease in pain, stiffness, and swelling, entirely through local action.

CORTRIL and TERRAMYCIN when used concurrently provide combined anti-inflammatory and anti-infectious therapy— a desirable as well as a useful precaution in many indications.

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Division, Chas. Pfizer & Co., Inc.

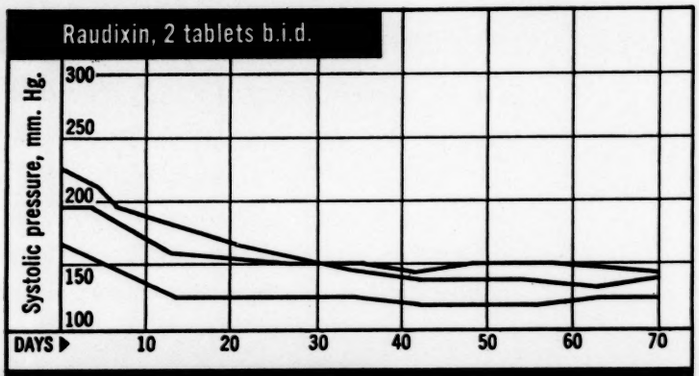
Pfizer

every patient with essential hypertension is a candidate for RAUDIXIN treatment

Because of its safety, RAUDIXIN is the drug to use first:

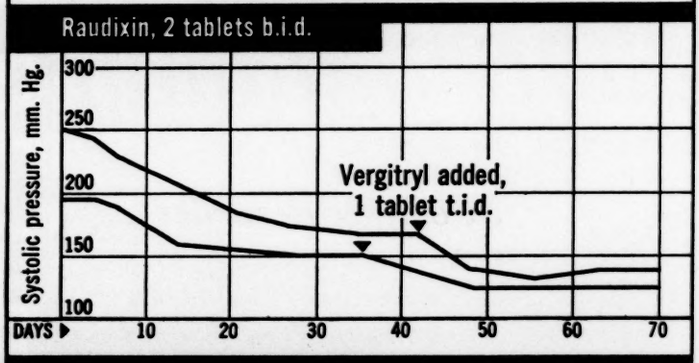
step 1

Raudixin controls most cases of mild to moderate hypertension, and some severe cases.



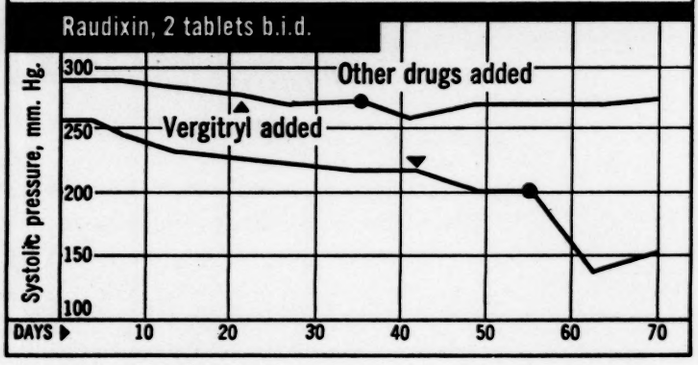
step 2

If blood pressure is not adequately controlled in four to eight weeks, Vergitryl (veratrum) may be added to Raudixin. This brings many of the remaining patients under control. Raudixin tends to delay tolerance to Veratrum, and makes smaller dosage possible.



step 3

For the few patients resistant to this combined regimen, a more potent drug may be added, for example, Bistrium (hexamethonium). The most potent drugs, which are potentially dangerous, are thus used only as a last resort in the most refractory cases.



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Squibb rauwolfia

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Bottles of 100 and 1000

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GANTRISIN + PENICILLIN

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Gantrisin 'Roche' "would seem to be an ideal sulfonamide to use where it is desirable to combine sulfonamide administration with other antibacterial agents."

Herrold, R. D.: South. Clin. North America *30*:61, 1950.

Also available—Gantricillin (100), containing 0.5 Gm Gantrisin and 100,000 units of crystalline penicillin G potassium.

Supplied: Bottles of 24, 100 and 500 tablets.

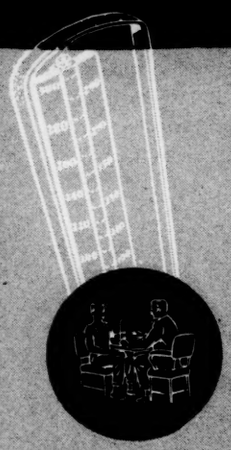
Gantricillin® Gantrisin®—brand of sulfisoxazole (3,4-dimethyl-5-sulfanilamido-isoxazole)

HOFFMANN-LA ROCHE INC • ROCHE PARK • NUTLEY 10 • N. J.

A New Concept of Treatment in Hypertension

Selection of Effective Drugs

TO FIT THE INDIVIDUAL PATIENT'S NEEDS



CRITICAL selection of drugs to fit the individual patient's needs has resulted in considerable progress in the management of the hypertensive patient. The approach to therapy can be rational and effective.

Whether the physician uses the criteria of Palmer, Loofbourow, and Doering;[1] those of Keith, Wagener, and Barker;[2] those of Smithwick,[3] or those of Pickell[4] for the evaluation of the patient's status, an armamentarium has been developed which permits of effective treatment in virtually every type and grade of the disease.

Two features are outstanding in this new concept of checking the patient's status against the drugs available:

A—No longer is it justified to withhold treatment from the patient with mild, labile hypertension, with or without symptoms. Today there is effective therapy for him, which gradually and safely lowers his blood pressure . . . gives him a new sense of tranquil well-being . . . rapidly overcomes any symptom flare-ups[5,6,7] . . . and bids well to prove effective in arresting or at least impeding further progress of the disease.

B—Broad clinical research and the resultant better understanding of hypotensive therapy have led to the development of drug combinations advantageous in treatment of more advanced or resistant cases. In these combinations, apparently through synergistic action, considerably smaller dosages of the potent hypotensives (as much as 50% less) deliver full therapeutic efficacy . . . make them effective in a higher percentage of patients . . . lessen the dangers inherent in some of them . . . reduce the incidence and severity of side actions . . . render successful treatment less difficult and less fraught with anxiety.[8,9,10]

Much of the advancement which recent years have seen in the management of hypertensive disease has been made available to the physician through research by Riker Laboratories. Among Riker "Firsts" are alkavervir, alseroxylon, and the combinations shown on the adjoining page.

There is...

---

1. Palmer, R.S.; Loofbourow, D., and Doering, C.R.: New England J. Med. *239*:990 (Dec.) 1948.
2. Keith, N.M.; Wagener, H.P., and Barker, N.W.: Am. J. M. Sc. *197*:332 (Mar.) 1939.
3. Smithwick, R.H.: Hypertension, A Symposium, edited by E.T. Bell, Minneapolis, University of Minnesota Press, 1951, pp. 429-448.
4. Pickell, F.W.: J. Louisiana M. Soc. *105*:393 (Oct.) 1953.
5. Vakil, R.J.: Brit. Heart J. *11*:350 (Oct.) 1949.
6. Wilkins, R.W.; Judson, W.E., and Stanton, J.R.: Proc. New England Cardiovas. Soc., 1951-1952, p. 34.
7. Ford, R.V.; Livesay, W.R.; Miller, S.I., and Moyer, J.H.: M. Rec. & Ann. *47*:608 (Aug.) 1953.
8. Wilkins, R.W., and Judson, W.E.: New England J. Med. *248*:48 (Jan. 8) 1953.
9. Ford, R.V., and Moyer, J.H.: Am. Heart J. *46*:754 (Nov.) 1953.
10. Ford, R.V., and Moyer, J.H.: GP *8*:51 (Nov.) 1953.

An Effective RIKER Preparation For Every Grade of the Disease

IN GRADE I

RAUWILOID

for Mild, Labile Hypertension

This selective alkaloidal extract (the alseroxylon fraction) of Rauwolfia serpentina provides effective treatment in the largest contingent of hypertensive patients, those with mild, labile hypertension. Rauwiloid produces:

- Moderate, gradual lowering of blood pressure—a slow, smooth, prolonged hypotensive effect . . .
- Rapid relief of symptoms, usually long before the full hypotensive effect is accomplished . . .
- Gentle sedation (a new type—without somnolescence)—a new sense of tranquility and well-being . . .
- Mild bradycardia, appreciated especially when tachycardia has led to anxiety . . .
- Virtually no side effects.

Rauwiloid retains the balanced activity of the several alkaloids of Rauwolfia serpentina in a purified, reproducible form. Effectiveness of Rauwiloid is assured by demonstrating in dogs the ability of each batch to produce the clinically desired hypotension, bradycardia, and sedation. Its action, centrally mediated, is exerted along physiologic channels. It is not adrenergic or ganglionic blockade, does not lead to postural hypotension.

Dosage is not critical, since increasing it beyond the minimum effective level produces but little increment of hypotensive effect or side actions. There are no known contraindications. Tolerance does not develop, hence maintenance does not require upward adjustments of dosage.

Dosage: One dose per day, initially 2 tablets (2 mg. each), taken on retiring, usually suffices; after full effect is reached, 1 tablet per day frequently is adequate for maintenance.

IN GRADES II and III

RAUWILOID + VERILOID

for Moderate to Severe Hypertension

The combination of Rauwiloid with the faster-acting, more potent hypotensive—Veriloid—provides effective therapy with least risk. Apparently potentiation of action makes smaller dosage of the more potent agent produce the desired hypotensive, symptom-relieving effects.

Each tablet of Rauwiloid+Veriloid presents 1 mg. of Rauwiloid and 3 mg. of Veriloid. Initial dose, 1 tablet t.i.d., best after meals. After 2 weeks, for establishment of Rauwiloid effect, dosage should be raised if required. Average maintenance dose, 1 tablet q.i.d.; some patients may require up to 2 tablets q.i.d.

At the effective dosage level the side actions to Veriloid (nausea or vomiting) are rarely encountered. In a high percentage of cases the combination provides rapid relief of associated symptoms, blood pressure is lowered, dosage adjustment is simplified, the patient gains a new sense of well-being, and—there is no danger of excessive hypotension. The addition of Rauwiloid greatly increases the percentage of patients in whom veratrum proves effective.

IN GRADES III and IV

RAUWILOID + HEXAMETHONIUM

for Intractable, Rapidly Progressing Hypertension

With this combination (each tablet contains Rauwiloid 1 mg. and hexamethonium 250 mg.) oral hexamethonium therapy becomes safer and easier to manage—a distinct advantage when the patient's status warrants the risk of using the most hypotensive mechanism—ganglionic blockade.

The full hypotensive effect of hexamethonium is realized from greatly reduced dosage (frequently up to 50% less), apparently because of synergistic action with Rauwiloid. Associated symptoms quickly yield, tachycardia is relieved by the mild bradycardic action of Rauwiloid, and tranquility supervenes.

Cautions and contraindications are only those applying to hexamethonium; but diligent patient supervision and careful instruction of the patient remain mandatory.

Therapy should be initiated with ½ tablet q.i.d., not less than 4 hours apart, best after meals and on retiring. After two weeks, when Rauwiloid effect has been established, dosage should be increased by 1 tablet per day, but not oftener than twice weekly, until desired effect is obtained.

In Hypertensive Crises Encephalopathy—Eclampsia

Parenteral veratrum preparations provide for immediate control of the critical blood pressure; they should be followed by carefully selected, adequate oral therapy based on the prognostic features of the case.

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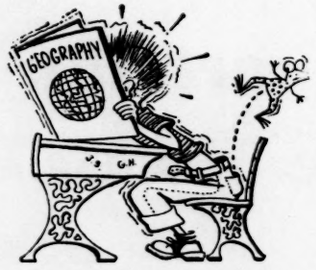
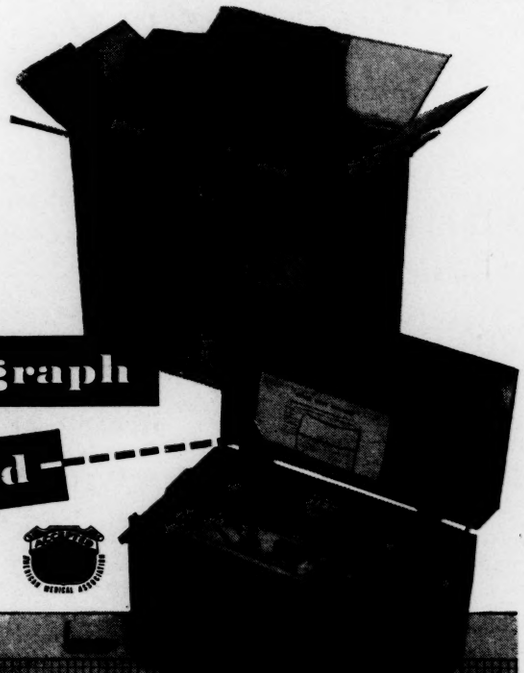


You can't always tell a book by its cover

● **The Viso-Cardiette's shipping carton is scientifically designed not only to provide safe transportation DIRECTLY to the user, but as the most convenient means for the instrument's RETURN to Sanborn Company, should it not be satisfactory after the no-obligation PRE-PURCHASE test.**



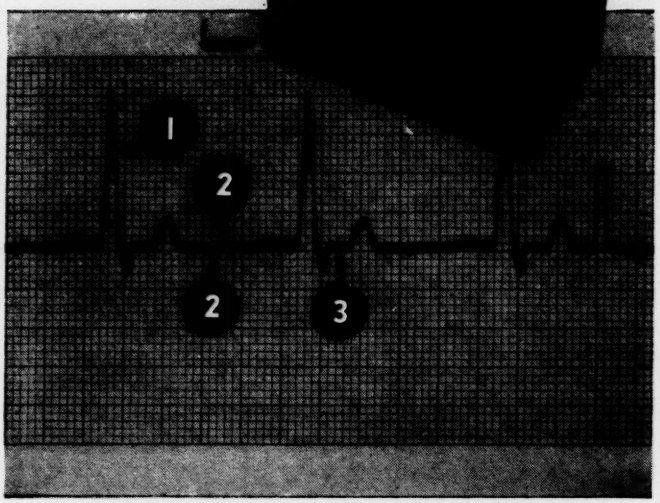
But you can tell an electrocardiograph by its record

A test record is taken on each Viso-Cardiette, just prior to packing for shipment, as final proof of its performance. This is Sanborn Company's way of assuring the new owner that his instrument will record *accurately* the actual potentials encountered in clinical electrocardiography.

The record shown at right is a specimen of these proving tests. Not of physiological origin, the wave forms registered in this record were produced by an electronic device in order that a *selected variety* of voltage forms could be applied to the Viso, through its patient cable, and in this way show on one record that the instrument's characteristics will suit these wave forms.

Of special note in this record are conclusive proofs of the Viso's complete suitability, such as (1) the clearly registered notch in the R wave, showing response to *rapid* fluctuations, (2) the tiny positive and negative deviations in the baseline, showing that a pulse as small as 0.02 mv can be recorded clearly at normal sensitivity levels, the level base line, and the S-T segment (3) recorded on the isoelectric line *as it actually existed in the applied voltage.*

Complete descriptive literature on the Viso-Cardiette, and details of an exclusive 15-day trial plan will be sent gladly on request.



In addition to providing UNDISTORTED INFORMATION, Viso-Cardiette records have these advantages . . .

- **They are in standard *rectangular coordinates*, which means *no* curvatures of complexes or time lines, or negative time intervals with which to contend.**
- **They may be standardized *during* leads, as well as before.**
- **Ordinarily, "AC" is eliminated *automatically* and *without* a ground wire by means of special circuits.**
- **The wide, ribbon-type baseline remains steady, even in locations where there is great fluctuation of line voltage.**

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In female breast carcinoma

Results of a recent clinical study show that Neodrol is effective in the palliative treatment of advanced, inoperable breast cancer in the female. Of the 42 patients (some with both soft tissue and osseous metastases) treated with Neodrol, 43% demonstrated objective improvement.

In soft tissue metastases	39% (14 of 37 pts.)	22% (38 of 174 pts.)
In osseous metastases	25% (8 of 32 pts.)	19% (26 of 133 pts.)

Pain	28	22
Anorexia	11	10
General Malaise	10	8
Cough	7	6
Dyspnea	13	8
Headache	6	6
Nausea	6	4
Vomiting	4	3

Of the 36 patients with symptoms referable to their carcinoma, a total of 87% experienced symptomatic improvement under Neodrol ther

Escher, G. C., et al.: Clinical Research Proceedings 1:51 (Apr.

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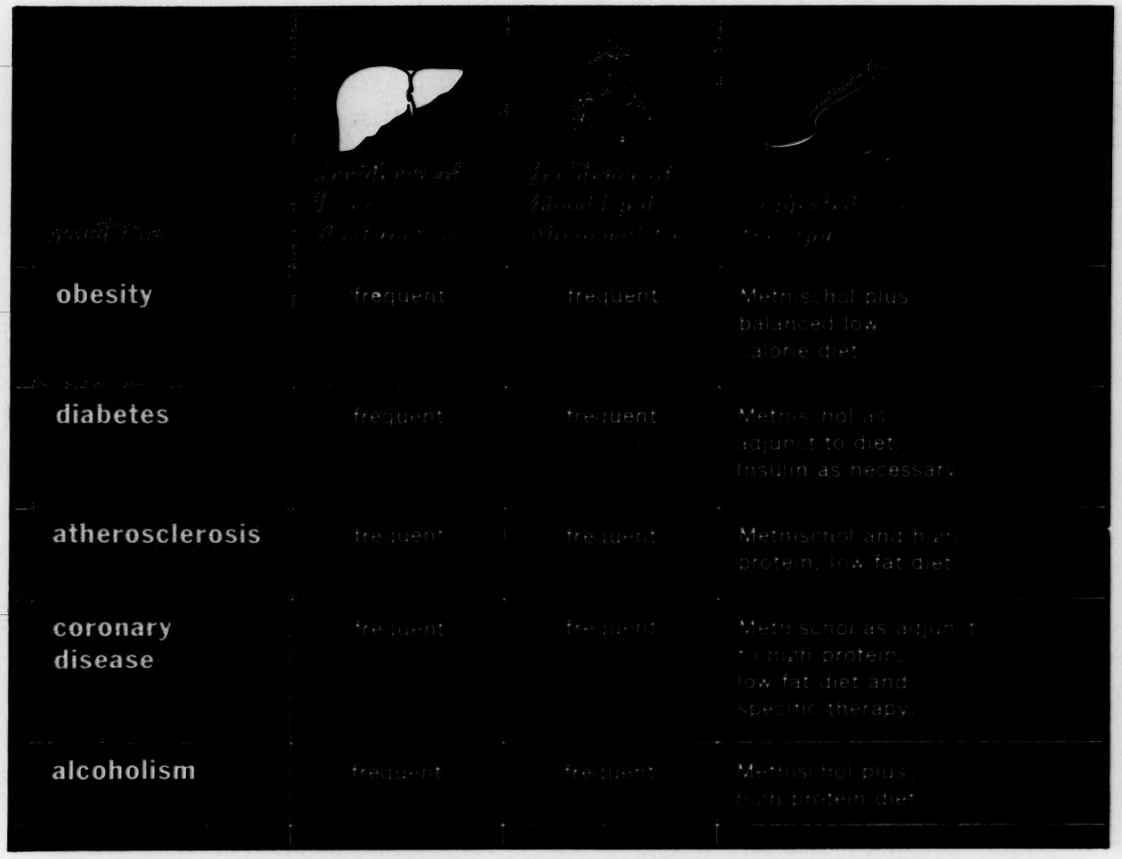

condition			
obesity	frequent	frequent	Methischol plus balanced low calorie diet
diabetes	frequent	frequent	Methischol as adjunct to diet. Insulin as necessary.
atherosclerosis	frequent	frequent	Methischol and high protein, low fat diet
coronary disease	frequent	frequent	Methischol as adjunct to high protein, low fat diet and specific therapy.
alcoholism	frequent	frequent	Methischol plus high protein diet

methischol

the complete lipotropic therapy

...because it provides vitamin B_{12} and liver fractions in addition to choline, methionine and inositol.

...helps normalize liver function, increase phospholipid turnover, reduce fatty deposits, and stimulate regeneration of new liver cells...

...helps reduce elevated cholesterol levels and chylomicron ratios towards the normal, and aids in achieving normal fat metabolism.

now— higher B_{12}

the suggested daily therapeutic dose of 9 capsules or 3 tablespoonfuls of Methischol provides:

Choline Dihydrogen Citrate*	2.5 Gm.
dl, Methionine	1.0 Gm.
Inositol	0.75 Gm.
Vitamin B_{12}	18 mcg.
Liver Concentrate and Desiccated Liver**	0.78 Gm.

*Present in syrup as 1.15 Gm. Choline Chloride
**Present in syrup as 1.2 Gm. Liver Concentrate

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the realization of a hope . . .

a new physio-chemical complex that consistently and significantly reduces elevated serum cholesterol levels.

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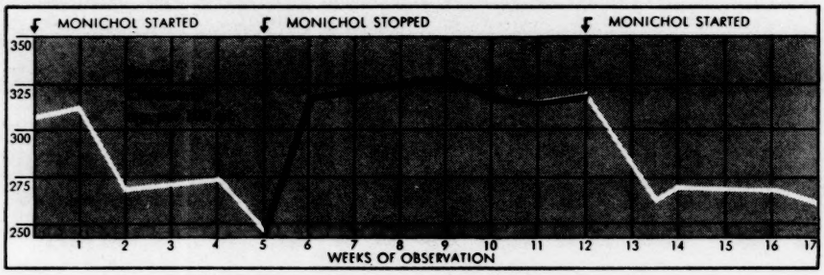
The investigators† stress the need for continued administration ot Monichol because idiopathic or familial hypercholesteremia is most probably an *inborn error of metabolism.*

Uninterrupted Daily Intake of Monichol
Essential in the Management of Hypercholesteremia



Please note the *prompt rise of the serum cholesterol to pre-treatment levels* when medication was stopped. We, therefore, urge you to ask your patients to have their prescriptions refilled as soon as their supply is exhausted.

Indications: For the therapeutic and prophylactic management of hypercholesteremia so frequently associated with cardiovascular disease and diabetes.

Dosage: The recommended dosage of 1 teaspoonful four times or two teaspoonfuls twice daily after meals is both the minimum and the optimum dosage.

Formula: Each teaspoonful (5 cc.) contains:

Polysorbate 80	500 mg.
Choline Dihydrogen Citrate	500 mg.
Inositol	250 mg.

Supplied: Bottles of 12 oz.

†Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. *152*:682 (June 20) 1953. *Trademark

Monichol normalizes cholesterol metabolism

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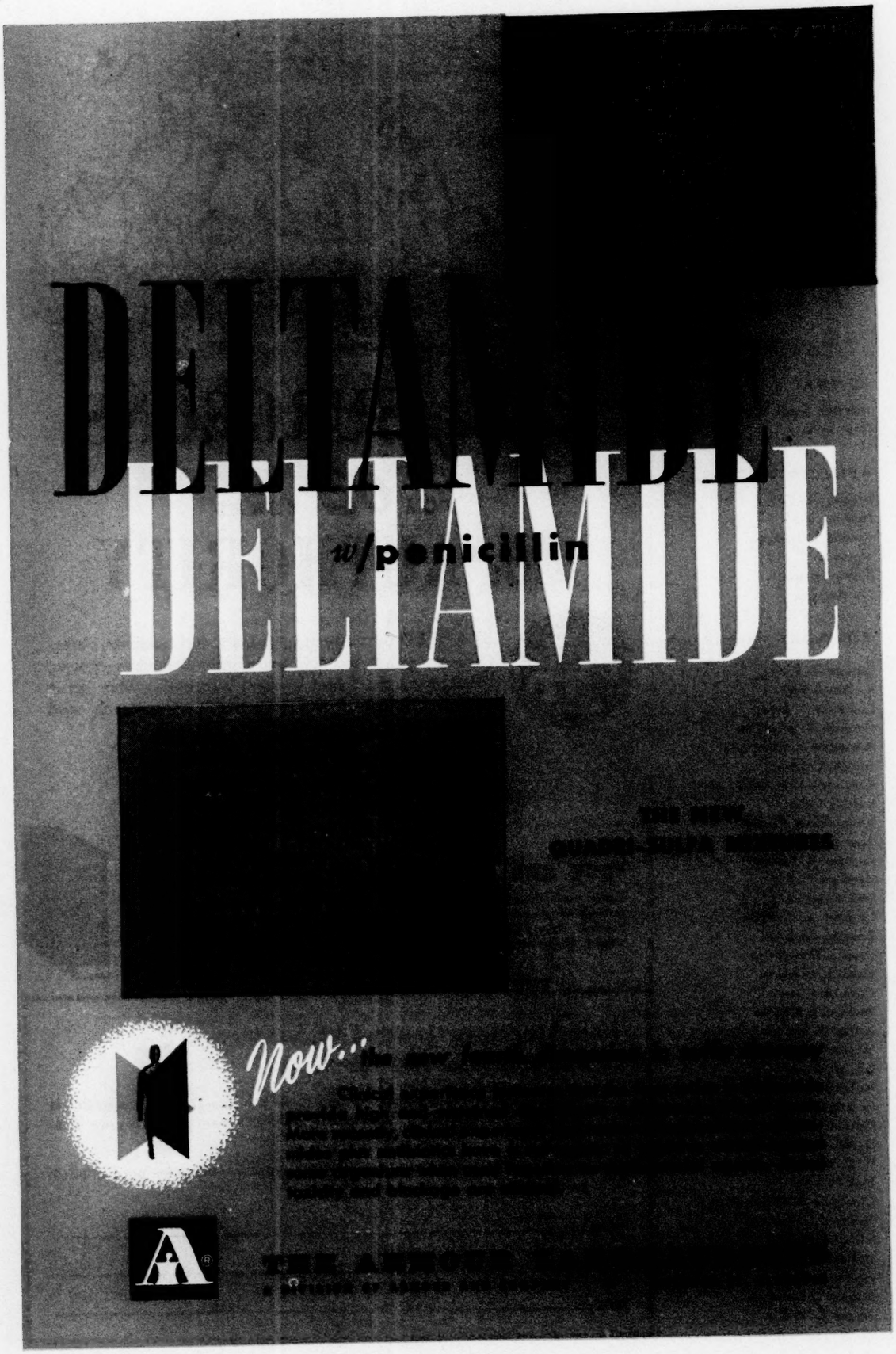
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Unitensen provides **cryptenamine,** the first—and only—isolated Veratrum alkaloid preparation which does not induce vomiting on the same (or approximate) dose as that which exerts hypotensive action.

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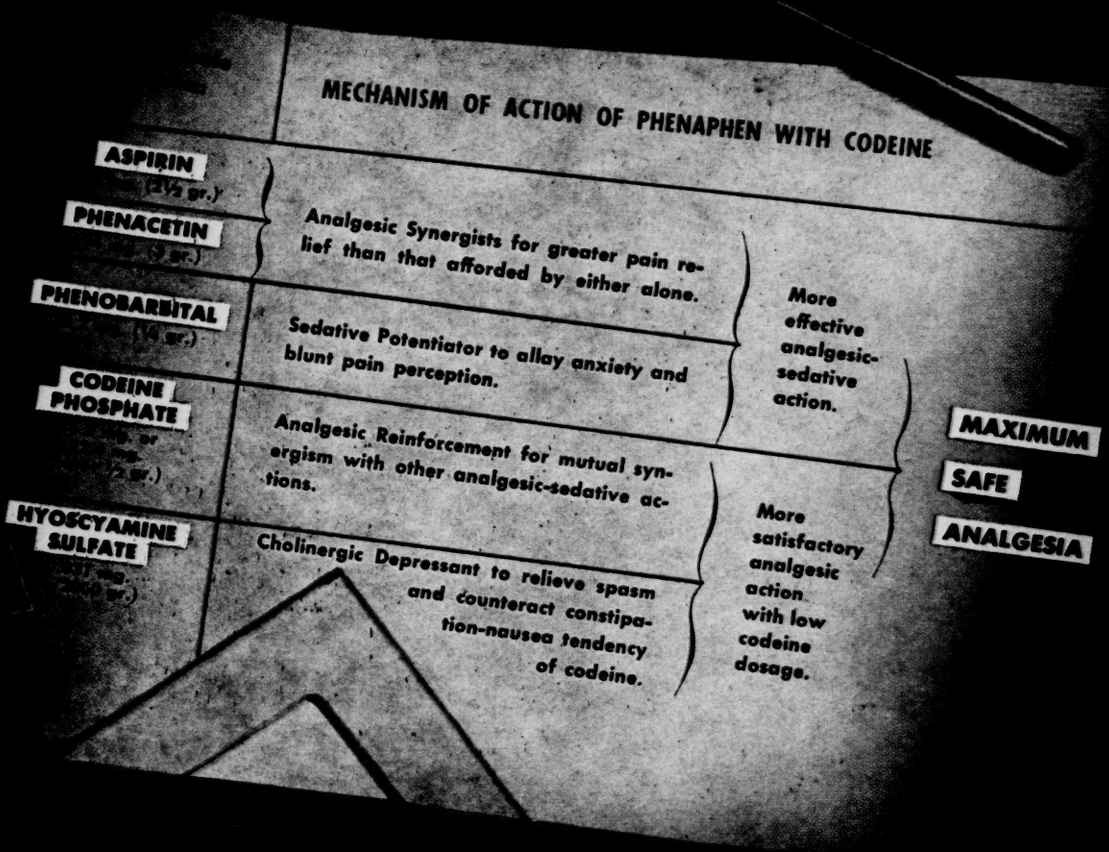

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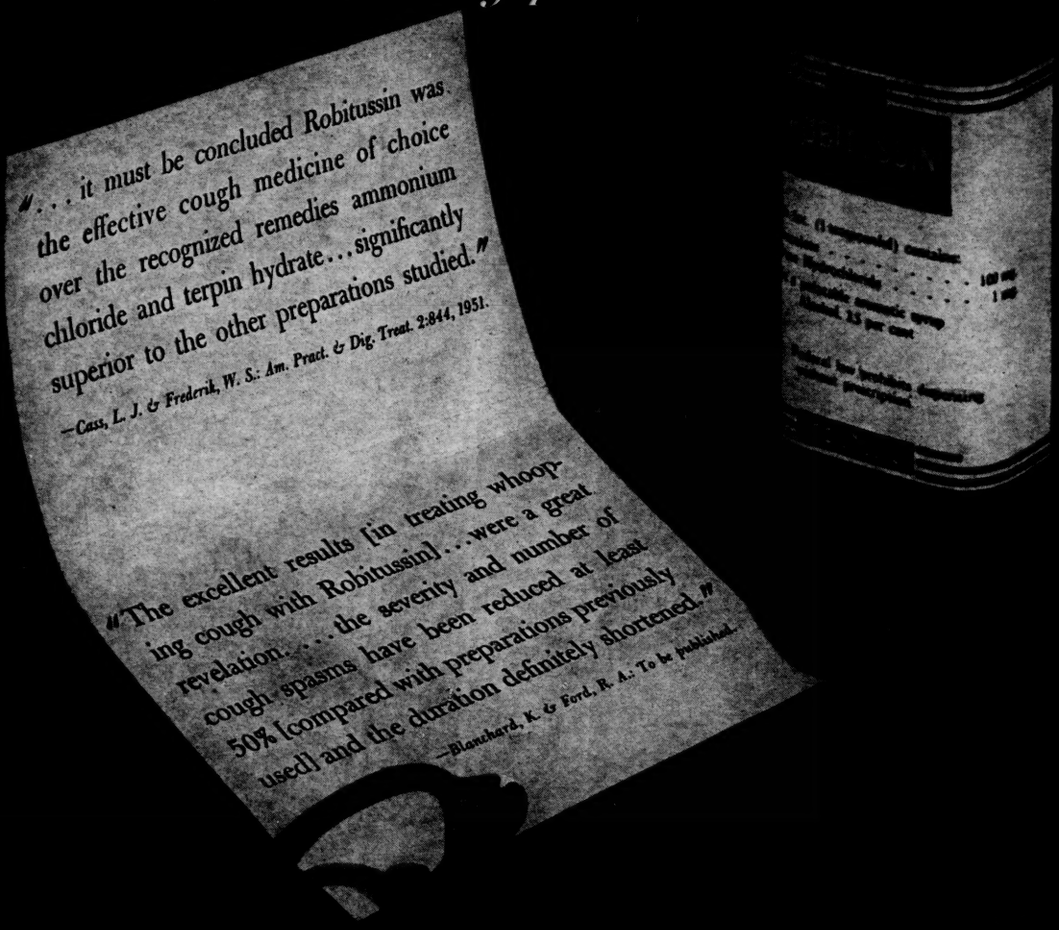

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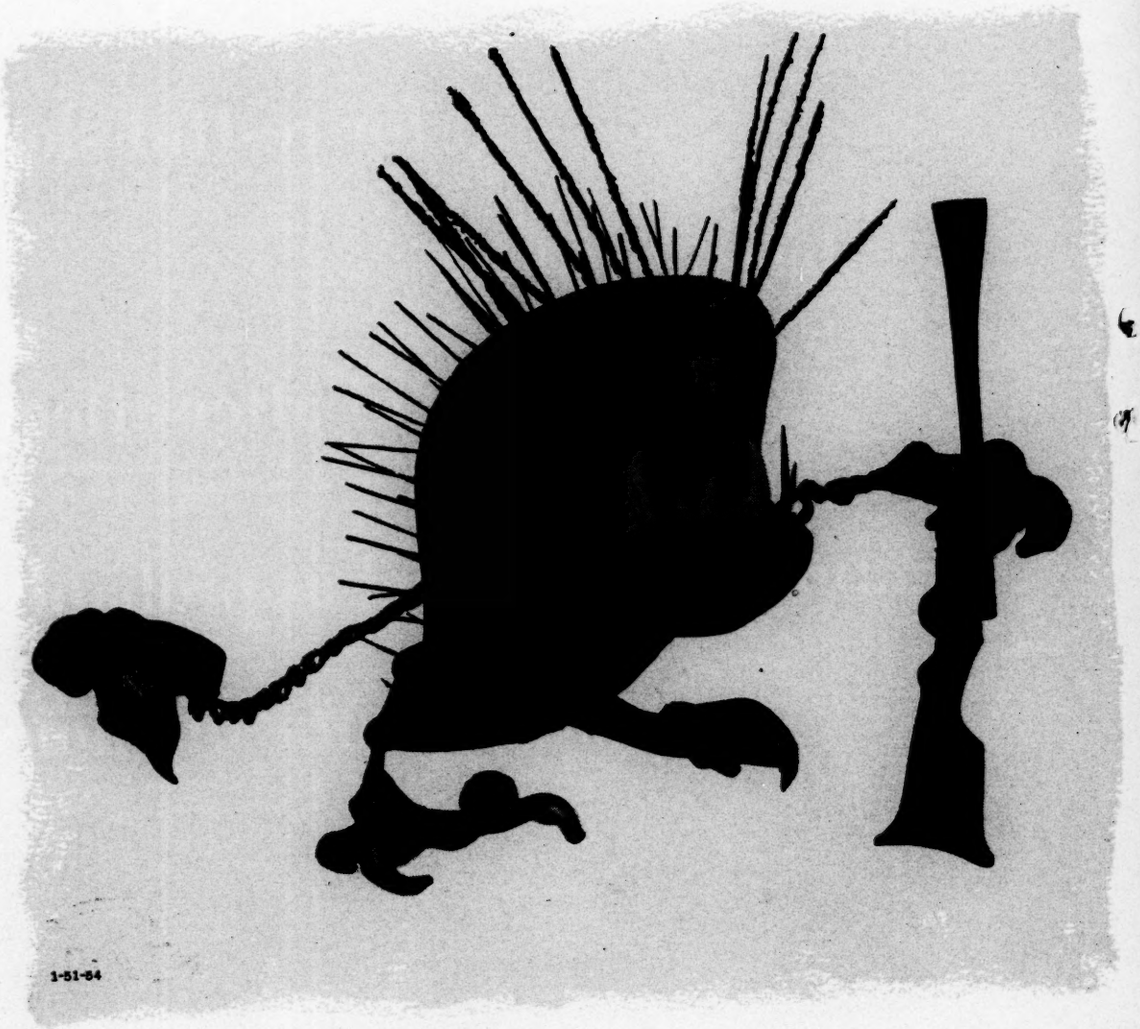

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against staphylococci, streptococci and pneumococci—especially indicated when patients are allergic to other antibiotics or when the organism is resistant.

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against staphylococci—because of the high incidence of staphylococci resistant to many other antibiotics.

A DRUG OF CHOICE

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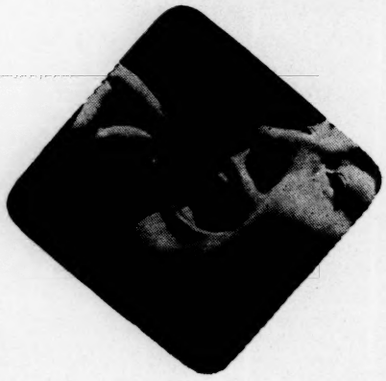

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